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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for Pediatric Myelomeningocele: Executive Summary

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Sponsored by: The Congress of Neurological Surgeons (CNS) and the Section on Pediatric Neurosurgery

Endorsed by: The Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS), the Spina Bifida Association (SBA)

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: The incidence of spina bifida (SB) in the developing world is higher than in the United States because of malnutrition and folic acid deficiency during pregnancy. Advances in technology have made prenatal repair of myelomeningocele (MM) possible.
OBJECTIVE: The objective of the guidelines are, (1) To create clinical recommendations for best practices, based on a systematic review and analysis of available literature, (2) to obtain multi-disciplinary endorsement of these guidelines from relevant organizations, and (3) to disseminate the educational content to physicians to improve the care of infants with MM.
METHODS: The Guidelines Task Force developed search terms and strategies used to search PubMed and Embase for literature published between 1966 and September 2016. Strict inclusion/exclusion criteria were used to screen abstracts and to develop a list of relevant articles for full-text review.
RESULTS: Guidelines authors aimed to systematically review the literature and make evidence based recommendations about the timing of closure after birth, hydrocephalus, the impact of prenatal closure, and the effect of prenatal closure on ambulation ability and tethered spinal cord. Evidence concerning persistent ventriculomegaly and cognitive impairment was also evaluated. Hundreds of abstracts were identified and reviewed for each of the 5 topics. A total of 14 studies met stringent inclusion criteria.
CONCLUSION: Based on a comprehensive systematic review, a total of 5 clinical practice recommendations were developed, with 1 Level I, 2 Level II and 2 Level III recommendations.
The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1.

KEY WORDS: Fetal, Guidelines, In utero, Myelomeningocele, Postnatal, Spina bifida, Tethered cord syndrome

Neurosurgery 85:299–301, 2019 DOI:10.1093/neuros/nyz261 www.neurosurgery-online.com

Spina bifida (SB) affects development and quality of life. Most infants with myelomeningocele (MM) have hydrocephalus (HC) and require surgical treatment. There are variations of clinical practice with regard to timing and type of closure, and antibiotic administration. While in utero closure of MM is an option for some women whose infants met certain criteria for diagnosis of SB as fetuses, globally, this option is not readily available. Some experts insert a ventriculoperitoneal shunt at birth, some advocate choroid plexus coagulation and endoscopic third ventriculostomies and others advocate conservative non-surgical management of HC and ventriculomegaly (VM).[1-3]

ABBREVIATIONS: AANS, American Association of Neurological Surgeons; **CNS,** Congress of Neurological Surgeons; **COI,** conflicts of interest; **HC,** hydrocephalus; **MM,** myelomeningocele; **MOMS,** Management of Myelomeningocele Study; **SB,** spina bifida; **VM,** ventriculomegaly

OBJECTIVES

Guidelines authors aimed to systematically review the literature and make evidence based recommendations about the timing of closure after birth, and to investigate the evidence concerning persistent VM and cognitive impairment.

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METHODOLOGY

Process Overview

The Guideline Task Force members conducted a systematic review of the literature relevant to the management of MM in infants and children. Additional details of the systematic review are provided at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1.

Selection of Clinical Topics

The goals of this effort were to discern the most effective strategies for a variety of MM-related problems, including timing of closure, antibiotics, and HC/ VM.

Literature Search

The search terms and strategies used to search The National Library of Medicine PubMed and Embase databases for relevant literature published between 1966 and September 2016 are available at https://www.cns.org/guidelines/guidelines-spina-bifida. Literature searches were supplemented with manual screenings of the bibliographies of all retrieved publications and other potentially relevant systematic reviews. All literature identified were subject to the article inclusion/exclusion criteria described at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1.

Rating the Quality of Evidence

The quality of evidence was rated using an evidence hierarchy developed by the Joint AANS/CNS Guidelines Review Committee for 3 different study types including therapeutic effectiveness and diagnosis and prognosis (Appendix II). Additional information regarding the hierarchy classification of evidence can be located here: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

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RECCOMMENDATIONS

PICO Question

Is there a difference in the proportion of patients who develop shunt-dependent HC between fetuses who underwent prenatal MM closure compared to infants who underwent postnatal MM repair?

Target Population

Infants with MM who meet eligibility criteria as fetuses for prenatal MM repair.

Recommendation(s)

Prenatal repair of MM is recommended for those fetuses who meet maternal and fetal Management of Myelomeningocele Study (MOMS) specified criteria for prenatal surgery to reduce the risk of developing shunt-dependent HC (Level I). Differences between prenatal and postnatal repair with respect to the requirement for permanent cerebrospinal fluid diversion should be considered along with other relevant maternal and fetal factors when deciding upon a preferred method of MM closure.

PICO Question

In patients with MM, does prenatal or postnatal closure improve the ability to ambulate?

Target Population

MM patients diagnosed prenatally.

RECOMMENDATION(S)

1. When possible, for prenatally diagnosed fetuses with MM who meet maternal and fetal MOMS inclusion criteria, prenatal closure of MM should be performed, which may improve ambulatory status for patients in the short term (at 30 mo of age) (Level II).
2. Long term benefit for ambulatory status with prenatal closure is unknown. Children who have had either prenatal or postnatal closure should be carefully followed for the development of tethered spinal cord with the associated loss of ambulatory function (Level III).

PICO Question

In patients born with a MM, does closure of the defect within 48 hours reduce the rate of infection?

Target Population

Infants born with a MM.

RECOMMENDATION(S)

1. There is insufficient evidence to confirm that closure of MMs within 48 hours decreases the risk of wound infection.

2. It is recommended that if MM closure is delayed beyond 48 hours, antibiotics should be initiated. (Level III)

PICO Question

In MM patients with HC, does persistent enlargement of the ventricles adversely impact neurocognitive development?

Target Population

MM patients with HC.

Recommendation

Currently, there is insufficient data to conclude that ventricular size and morphology impact neurocognitive development.

PICO Question

Is there a difference in the rate of development of tethered cord syndrome in infants who had prenatal MM closure compared to infants who had MM closure after birth?

Target Population

Infants and children with MM.

Recommendation(s)

Continued surveillance for tethered cord syndrome and/or the development of inclusion cysts in children with prenatal and postnatal closure of MM is indicated (Level II), as there is evidence that prenatal closure increases the risk of recurrent tethered cord over the baseline rate seen with postnatal closure.

CONCLUSION

This evidence based guideline and systematic review of the literature relevant to children with MM were accomplished in order to improve the quality of life for patients with MM.

Disclosures

These evidence-based clinical practice guidelines were funded exclusively by the CNS, which received no funding from outside commercial sources to support the development of this document.

Conflicts of Interest

All Guideline Task Force members were required to disclose all potential conflicts of interests (COIs) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See Appendix I for a complete list of disclosures.

Disclaimer of Liability

This clinical, systematic, evidence-based clinical practice guideline was developed by a multi-disciplinary physician volunteer taskforce and is provided as an educational tool based on an assessment of the current scientific and clinical information regarding the management and treatment of pediatric patients with MM. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Acknowledgments

The guidelines task force would like to acknowledge the CNS Guidelines Committee for their contributions throughout the development of the guideline, the AANS/CNS Joint Guidelines Review Committee, as well as the American Academy of Pediatrics, Child Neurology Society and Spina Bifida Association for their review, comments, and suggestions throughout peer review, as well as the contributions of Trish Rehring, MPH, CHES, Senior Manager of Clinical Practice Guidelines for the CNS, and Gretchen Kuntz, MSW MLIS, for assistance with the literature searches. Throughout the review process, the reviewers and authors were blinded from one another. At this time the Guidelines Task Force would like to acknowledge the following individual peer reviewers for their contributions: Kimon Bekelis, MD; Robin Bowman, MD; Timothy J. Brei, MD; Andrew P Carlson, MD; John Chi, MD; Mark Dias, MD; Jeffrey Olson, MD; John O'Toole, MD; Michael Partington, MD; Curtis Rozzelle, MD; Krystal Tomei, MD; and Jan B. Wollack, MD, PhD.

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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Incidence of Shunt-Dependent Hydrocephalus in Infants With Myelomeningocele After Prenatal Versus Postnatal Repair

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: Myelomeningocele (MM) is a condition that is responsible for considerable morbidity in the pediatric population. A significant proportion of the morbidity related to MM is attributable to hydrocephalus and the surgical management thereof. Postnatal repair remains the most common form of treatment; however, increased rates of prenatal diagnosis, advances in fetal surgery, and a hypothesis that neural injury continues in utero until the MM defect is repaired have led to the development and evaluation of prenatal surgery as a means to improve outcomes in afflicted infants.

OBJECTIVE: The objective of this guideline is to systematically evaluate the literature to determine whether there is a difference in the proportion of patients who develop shunt-dependent hydrocephalus in infants who underwent prenatal MM repair compared to infants who had postnatal repair.

METHODS: The Guidelines Task Force developed search terms and strategies used to search PubMed and Embase for relevant literature published between 1966 and September 2016. Strict inclusion/exclusion criteria were used to screen abstracts and to develop a list of relevant articles for full-text review. Full-text articles were then reviewed, and when appropriate, included as evidence.

RESULTS: A total of 87 abstracts were identified and reviewed by 3 independent reviewers. Thirty-nine full-text articles were selected for analysis. Three studies met selection criteria and were included in the evidence table.

CONCLUSION: Class I evidence from 1 study and class III evidence from 2 studies suggest that, in comparison to postnatal repair, prenatal surgery for MM reduces the risk of developing shunt-dependent hydrocephalus. Therefore, prenatal repair of MM is recommended for those fetuses who meet specific criteria for prenatal surgery to reduce the risk of developing shunt-dependent hydrocephalus (level I). Differences between prenatal and postnatal repair with respect to the requirement for permanent cerebrospinal fluid diversion should be considered alongside other relevant maternal and fetal factors when deciding upon a preferred method of MM closure.

The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-2.

KEY WORDS: Fetal, Hydrocephalus, In utero closure, Myelomeningocele, Postnatal, Shunt, Spina bifida

Neurosurgery 85:E405–E408, 2019 DOI:10.1093/neuros/nyz262 www.neurosurgery-online.com

The approximate incidence of myelomeningocele (MM) in the United States is 3.4 per 10 000 live births.[1] Live-born infants with MM have an approximately 10% risk of mortality, and survivors face significant morbidity.[2,3]

ABBREVIATIONS: COI, conflict of interest; **CSF,** cerebrospinal fluid; **MM,** myelomeningocele; **MOMS,** Management of Myelomeningocele Study

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Conventional treatment of MM has been to perform a postnatal repair within 48 h after birth. After repair of the defect, neurosurgeons must remain vigilant about recognizing and treating hydrocephalus, which is a frequent comorbidity in MM patients.

Early observations regarding the effect of prenatal MM repair on outcomes were published in the 1990s,[4-6] and demonstrated that some fetuses who received in utero repair had improved functional outcomes and a lower requirement for shunt placement after birth. Outcomes in subsequent larger cohorts of infants who were treated with prenatal surgery as fetuses, when compared to historical controls treated with postnatal repair, continued to demonstrate evidence of improved patient functional outcomes and a lower incidence of shunt-dependent hydrocephalus.[6,7]

Prenatal repair of MM involves serious and permanent risks for mother and fetus. Fetal demise, preterm labor, premature rupture of membranes, and maternal infection are of particular concern. The Management of Myelomeningocele Study (MOMS) trial was the first and only randomized comparison of the safety and efficacy of prenatal MM repair with respect to conventional postnatal surgery.[8]

No evidence-based guidelines regarding the role of prenatal surgery in the management of MM were published prior to this guideline. Given the potentially important risks and benefits to the infant and mother, the authors felt that it was important to evaluate the literature in a systematic way in an effort to guide clinicians in the management of this challenging disorder. In this guideline, the authors specifically address whether the incidence of shunt-dependent hydrocephalus differs between fetuses with MM who underwent prenatal vs infants with MM who underwent postnatal repair.

METHODS

The task force members collaborated with a medical librarian to search the PubMed and Embase databases for the period from 1966 to September 2016. The literature search yielded 71 abstracts. To supplement the results of the electronic search, an additional 16 abstracts/articles were identified after manually screening the bibliographies of all retrieved publications. The task force selected 39 full-text articles for review. Of these, 36 were rejected for not meeting inclusion criteria or for being off-topic. Three were selected for systematic review and inclusion into the evidence tables.[9-11]

The quality of evidence was rated using an evidence hierarchy for therapeutic studies. Demonstrating the highest degree of clinical certainty, class I evidence is used to support recommendations of the strongest type, defined as level I recommendations. Level II recommendations reflect a moderate degree of clinical certainty and are supported by class II evidence. Level III recommendations denote clinical uncertainty supported by class III evidence.

Additional information about the methods utilized in this systematic review is provided in the introduction and methodology chapter (https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1).

RECOMMENDATIONS

PICO Question: Is there a difference in the proportion of patients who develop shunt-dependent hydrocephalus between fetuses who underwent prenatal MM closure compared to infants who underwent postnatal MM repair?

Target Population: Infants with MM who meet eligibility criteria as fetuses for prenatal MM repair.

Recommendation(s): Prenatal repair of MM is recommended for those fetuses who meet maternal and fetal MOMS specified criteria for prenatal surgery to reduce the risk of developing shunt-dependent hydrocephalus (level I). Differences between prenatal and postnatal repair with respect to the requirement for permanent cerebrospinal fluid (CSF) diversion should be considered alongside other relevant maternal and fetal factors when deciding upon a preferred method of MM closure.

DISCUSSION

There appears to be evidence that prenatal MM repair is effective in reducing the proportion of infants who require CSF shunt placement when compared to infants who are treated using conventional postnatal repair.[8-11] The most robust data come from a single randomized controlled trial, although there is other evidence in support of the direction and magnitude of the observed effect. Based on a thorough systematic review of the literature, this guideline can provide a level I recommendation that prenatal repair of MM is recommended for those fetuses that meet maternal and fetal MOMs inclusion criteria to reduce the risk of developing shunt-dependent hydrocephalus. Differences between prenatal and postnatal repair with respect to the requirement for permanent CSF diversion should be considered alongside other relevant maternal and fetal factors, such as the likelihood of preterm delivery, when deciding upon a preferred method of MM closure.

Biases inherent to small cases series limit the quality of the data they can provide. Nevertheless, the foundation of the current recommendation can be somewhat strengthened if these case

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series provide data which are congruent with more methodologically rigorous studies. Several case series, with or without the use of historical controls, were identified during the process of initial abstract screening. Although they did not meet the criteria for inclusion into the evidence table, they do provide some corroborating information relevant to this recommendation.

Two studies employed historical controls treated with postnatal repair as a benchmark to evaluate the effect of prenatal MM closure on the requirement for shunt placement.[6,7] Both of these studies provided supportive evidence in favor of the magnitude and direction of the effect observed in the subsequently completed MOMS.

Several retrospective, noncomparative cases series provided evidence regarding the proportion of patients who required CSF shunt placement following either postnatal[12-17] or prenatal[18,19] MM repair. The results of these small studies report shunt placement rates generally around 80% in postnatal repair infants and 50% in prenatal repair patients, largely in keeping with the eventual results of the MOMS trial.[8,10] As emphasized by the MOMS investigators, the lack of uniform criteria for the initiation of permanent CSF diversion therapy can significantly influence the likelihood of this outcome. To illustrate this point further, by using rigorous and "stringent" criteria for the placement of a CSF shunt, clinicians at Great Ormond Street Hospital were able to demonstrate that the shunt insertion rate in a contemporary cohort who underwent postnatal MM repair could be lower than previously reported and comparable to that following in utero repair.[14]

Despite the strength of the recommendation, readers of this guideline should be cognizant of important caveats regarding generalizability. This recommendation is based upon data from a very small number of patients because of the highly restrictive criteria that are used to judge whether an individual is appropriate for prenatal intervention. As a corollary, the recommendation is only applicable to patients who are considered potential candidates for prenatal MM repair based upon those same criteria. In addition, there is uncertainty regarding whether the documented effect of prenatal MM repair on the incidence of shunt dependent hydrocephalus can be replicated outside of the highly experienced centers involved in MOMS. This issue further limits the potential impact of this recommendation to the general MM population.

CONCLUSION

Class I evidence from 1 study and class III evidence from 2 studies suggest that in comparison to postnatal repair, prenatal surgery for MM reduces the risk of developing shunt-dependent hydrocephalus. Therefore, prenatal repair of MM is recommended for those infants who meet specific criteria for prenatal surgery as fetuses to reduce the risk of developing shunt-dependent hydrocephalus (level I). Differences between prenatal and postnatal repair with respect to the requirement for permanent CSF diversion should be considered alongside other relevant maternal and fetal factors when deciding upon a preferred method of MM closure.

Disclosures

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Conflict of Interest

The Guidelines Task Force members were required to report all possible COIs (conflicts of interest) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The COI findings are provided in detail in the companion introduction and methods manuscript (https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1).

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Acknowledgments

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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Management of Patients With Myelomeningocele: Whether Prenatal or Postnatal Closure Affects Future Ambulatory Status

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: Myelomeningocele (MM) is an open neural tube defect treated by pediatric neurosurgeons with prenatal or postnatal closure.

OBJECTIVE: The objective of this systematic review was to answer the question: What is the evidence for the effectiveness of prenatal vs postnatal closure of MM regarding short and long-term ambulatory status? Treatment recommendations were provided based on the available evidence.

METHODS: The National Library of Medicine PubMed database and Embase were queried using MeSH headings and keywords relevant to ambulatory status after prenatal or postnatal closure of MM. Abstracts were reviewed to identify which studies met the inclusion criteria. An evidence table was assembled summarizing the studies and the quality of evidence (Classes I-III). Based on the quality of the literature, a recommendation was rendered (Level I, II, or III).

RESULTS: One randomized controlled trial (Class II) and 3 retrospective cohort studies (Class III) were included as evidence. Initial ambulatory status depended on anatomic level of the neural tube defect. In the short term, prenatal closure may improve ambulatory status compared to postnatal closure. Spinal cord tethering or dermoid inclusion cyst has been associated with neurologic deterioration in infants closed in utero and after birth. Ambulation may cease in both groups over time. No long-term studies evaluated whether there is a difference in the ability to ambulate upon reaching adulthood.

CONCLUSION: Prenatal closure of MM may improve ambulatory status in the short term (Level II). Spinal cord tethering in both groups caused deterioration in the ability to walk. Evaluation and treatment of spinal cord tethering may help maintain ambulatory status (Level III). No studies evaluate whether prenatal or postnatal repair provides improved ability to ambulate upon reaching adulthood.

The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-3.

KEY WORDS: Ambulation, Evidence, Fetal, Fetoscopic, In utero, Myelomeningocele, Spina bifida

Neurosurgery 85:E409–E411, 2019 DOI:10.1093/neuros/nyz263 www.neurosurgery-online.com

Myelomeningocele (MM), or open neural tube defect, is a condition often diagnosed prenatally with fetal ultrasound or maternal blood test. The current incidence of MM is approximately 3 per 10 000 live births (according to the Center for Disease Control), with around 1500 babies born with spina bifida each year in the United States.[1] The incidence was much higher prior to the United States' government recommendations in 1992 and 1996 to supplement women's diet with folic acid.[1] Historically, postnatal closure

ABBREVIATIONS: AANS, American Association of Neurological Surgeons; **COI,** conflict of interest; **CNS,** Congress of Neurological Surgeons; **MM,** myelomeningocele

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was performed to prevent central nervous system infection. With the advent of technology to perform fetal surgery, current options for initial treatment include prenatal and postnatal closure. It is unknown whether there is a benefit for ambulatory status of patients with prenatal versus postnatal closure.

The objective of this systematic review is to evaluate the effect of prenatal closure compared to postnatal closure of the neural placode on the ability to ambulate in patients born with MM. Intended users of these guidelines include medical professionals who treat patients with MM, including providers in the prenatal setting who provide counseling treatment options and those in the postnatal setting regarding prognosis.

METHODS

The Guidelines Task Force initiated a systematic review of the literature and evidence-based guideline relevant to the diagnosis and treatment of patients with MM. Additional information about the methods utilized in this systematic review is provided in the introduction and methodology chapter (https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1). The Guidelines Task Force worked with a research librarian to develop search strategies for relevant literature published between 1966 and September 2016 in PubMed and Embase. The literature search yielded 30 abstracts. There were 4 full-text articles[2-5] that met inclusion criteria (see Appendix IV). See PRISMA Article Flow Chart in Appendix II.

Rating and Classification of the Quality of Evidence

Demonstrating the highest degree of clinical certainty, Class I evidence is used to support recommendations of the strongest type, defined as Level I recommendations. Level II recommendations reflect a moderate degree of clinical certainty and are supported by Class II evidence. Level III recommendations denote clinical uncertainty supported by Class III evidence. Additional information regarding the hierarchy classification of evidence is found on the CNS Guidelines Procedures and Policies page at: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RECOMMENDATIONS

PICO Question: In patients with MM, does prenatal or postnatal closure improve the ability to ambulate?
Target Population: MM patients diagnosed prenatally.

Recommendation(s)

1. When possible, for prenatally diagnosed fetuses with MM who meet maternal and fetal Management of Myelomeningocele Study inclusion criteria, prenatal closure of MM should be performed, which may improve ambulatory status for patients in the short term (at 30 mo of age) (Level II).
2. Long term benefit for ambulatory status with prenatal closure is unknown. Children who have had either prenatal or postnatal closure should be carefully followed for the development of tethered spinal cord with the associated loss of ambulatory function (Level III).

CONCLUSION

Based on the criteria for the classification of evidence on therapeutic effectiveness (Appendix III), prenatal closure of MM may improve ambulatory status in the short term (Level II recommendation). Spinal cord tethering in both groups caused deterioration in the ability to walk. Children who have had either prenatal or postnatal closure should be carefully followed for the development of tethered spinal cord with the associated loss of ambulatory function (Level III recommendation). No studies evaluate whether prenatal or postnatal repair provides improved ability to ambulate upon reaching adulthood.

Disclosures

These evidence-based clinical practice guidelines were funded exclusively by the CNS, which received no funding from outside commercial sources to support the development of this document.

Conflict of Interest

The Guidelines Task Force members were required to report all possible conflicts of interests (COIs) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The COI findings are provided in detail in the companion introduction and methods manuscript (https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1).

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These

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guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Acknowledgments

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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Closure of Myelomeningocele Within 48 Hours to Decrease Infection Risk

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: Appropriate timing for closure of myelomeningocele (MM) varies in the literature. Older studies present 48 h as the timeframe after which infection complication rates rise.

OBJECTIVE: The objective of this guideline is to determine if closing the MM within 48 h decreases the risk of wound infection or ventriculitis.

METHODS: The Guidelines Task Force developed search terms and strategies used to search PubMed and Embase for relevant literature published between 1966 and September 2016. Strict inclusion/exclusion criteria were used to screen abstracts and to develop a list of relevant articles for full-text review. Full text articles were then reviewed and when appropriate, included in the evidentiary table. The class of evidence was evaluated, discussed, and assigned to each study that met inclusion criteria.

RESULTS: A total of 148 abstracts were identified and reviewed. A total of 31 articles were selected for full text analysis. Only 4 of these studies met inclusion criteria.

CONCLUSION: There is insufficient evidence that operating within 48 h decreases risk of wound infection or ventriculitis in 1 Class III study. There is 1 Class III study that provides evidence of global increase in postoperative infection after 48 h, but is not specific to wound infection or ventriculitis. There is 1 Class III study that provides evidence if surgery is going to be delayed greater than 48 h, antibiotics should be given.

The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-4.

KEY WORDS: Fetal, Infection, Meningitis, Myelomeningocele, Surgery, Ventriculitis

Neurosurgery 85:E412–E413, 2019 DOI:10.1093/neuros/nyz264 www.neurosurgery-online.com

The optimum timing of myelomeningocele (MM) closure has been debated in the literature. The benefits of early closure have been touted to decrease risk of infection. However, there is concern that these infants can be ill and the situation overwhelming to the family, therefore delaying closure may be warranted. In this guideline, the authors address whether the literature clearly shows there to be a decreased risk of infection with closure within 48 h.

ABBREVIATIONS: COI, conflicts of interest; **MM,** myelomeningocele

METHODS

The Guidelines Task Force initiated a systematic review of the literature and evidence-based guideline relevant to the diagnosis and treatment of patients with MM. Additional information about the methods utilized in this systematic review is provided in the introduction and methodology chapter (https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1).

A series of authors for the development of guidelines related to MM were identified and screened for conflict of interest. This group, in turn, agreed on a set of pertinent questions to address the topic at hand, and conducted a systematic review of the literature relevant to MM. The recommendations deliberately eschewed the use of expert opinion, and instead relied strictly on the available literature.

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Literature Search

The Guidelines Task Force worked with a research librarian to assist with the formulation of search terms related to MM, time to surgery, complications, and infection used to search PubMed and Embase for relevant literature published between 1966 and September 2016. Co-authors used the article inclusion/exclusion criteria described below to screen 148 abstracts and provide a list of 31 relevant articles for full-text review. Staff compiled the results for review and final approval by all the task force members. All literature identified by searches of the electronic databases was subject to the article inclusion/exclusion criteria listed below. The search strategies used are provided within the methods sections of the topics evaluated below.

Of the 31 articles selected, 27 were rejected for not meeting inclusion criteria or for being off-topic. There were 4 studies that met inclusion criteria (see Appendix IV).[1-4] See PRISMA Article Flow Chart in Appendix II.

Rating Quality of Evidence

Demonstrating the highest degree of clinical certainty, Class I evidence is used to support recommendations of the strongest type, defined as Level I recommendations. Level II recommendations reflect a moderate degree of clinical certainty and are supported by Class II evidence. Level III recommendations denote clinical uncertainty supported by Class III evidence. Additional information regarding the hierarchy classification of evidence can be located here: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RECOMMENDATIONS

- There is insufficient evidence to confirm that closure of MMs within 48 h decreases the risk of wound infection.
- It is recommended that if MM closure is delayed beyond 48 h, antibiotics should be initiated (Level III).

CONCLUSION

In conclusion, there is insufficient evidence to support that closing MMs within 48 h decreases the rate of wound infection and ventriculitis. However, if the MM closure is going to be delayed, antibiotics should be initiated.

Disclaimer of Liability

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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Management of Patients With Myelomeningocele: Whether Persistent Ventriculomegaly Adversely Impacts Neurocognitive Development

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: Myelomeningocele (MM) is the most common congenital anomaly to affect the nervous system and affects 1500-2000 newborn infants per year in the United States. It is accompanied by symptomatic hydrocephalus in approximately 70%-80% of patients. Different treatment strategies for hydrocephalus characteristically result in different effects on the size of the ventricles.

OBJECTIVE: The objective of this systematic review was to determine whether persistent ventricular enlargement adversely impacts neurocognitive development in patients with MM.

METHODS: The PubMed National Library of Medicine Medline database and Embase were queried using MeSH headings and keywords relevant to neurocognitive or intellectual development and ventricular size or morphology. Abstracts were reviewed by the authors to identify which studies met strict inclusion criteria. An evidence table was constructed that summarized the included studies and reflected the quality of evidence (Classes I–III) that each represented. A recommendation was made that is based on the quality of the evidence.

RESULTS: An initial abstract review utilizing strict inclusion/exclusion criteria yielded 48 studies, 9 of which underwent full-text review. There is limited and conflicting Class III evidence from 2 studies.

CONCLUSION: Currently, there is insufficient data to conclude that ventricular size and morphology impact neurocognitive development.

The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-5.

KEY WORDS: Cognition, Development, Hydrocephalus, In utero, Myelomeningocele, Fetal, Ventriculomegaly

Neurosurgery 85:E414–E416, 2019 DOI:10.1093/neuros/nyz265 www.neurosurgery-online.com

Hydrocephalus requiring surgical intervention occurs in 70%-80% of children with myelomeningocele (MM).[1] Shunts have been highly effective in the treatment of hydrocephalus, but are also plagued by high morbidity due to shunt blockage, shunt infection, shunt fracture, disconnection, or shunt over-drainage. Despite innovation and extensive trials of improving shunt design, these complications of shunting occur at significant levels at virtually all centers that provide care. Furthermore, shunts are not available in all countries, due to cost and limited availability.

Due to these challenges, a variety of alternate treatments for symptomatic hydrocephalus in patients with MM have been proposed. Some centers advocate a less aggressive approach to the treatment of patients with ventriculomegaly associated with MM.[2,3] Infants with asymptomatic ventriculomegaly are closely

ABBREVIATIONS: CPC, choroid plexus coagulation; **ETV,** endoscopic third ventriculostomy; **MM,** Myelomeningocele; **WISC-R,** Wechsler Intelligence Scale for Children-Revised

monitored for progressive macrocephaly, signs of neurological dysfunction and/or progressive ventricular enlargement. In the absence of these concerns, children with asymptomatic ventriculomegaly may not be offered surgical treatment and are often managed conservatively.

Another important alternative treatment is an endoscopic third ventriculostomy (ETV) with or without choroid plexus coagulation (CPC).[4] However, ETV/CPC has retained its popularity due to its freedom from shunt dependency (with associated high shunt failure morbidity) and reduced cost. One characteristic of ETV/CPC is that the ventricles often remain enlarged even in procedures that are clinically effective at reducing raised intracranial pressure.

These recent management strategies of infants with MM often result in persistent ventriculomegaly. The long-term effects of chronic ventriculomegaly on neurocognitive development in these infants have not been determined.

METHODS

The Guidelines Task Force initiated a systematic review of the literature and evidence-based guideline relevant to the diagnosis and treatment of patients with MM. The task force members collaborated with a medical librarian to search the PubMed National Library of Medicine Medline database and Embase Database for the period from 1966 to September 2016 using the search strategies provided in Appendix I. The literature search yielded 44 original papers. An additional bibliography search of these candidate papers revealed an additional 4 candidate papers resulting in 48 total abstracts. Based on inclusion/exclusion criteria detailed below, the task force selected 9 articles for full review. Seven[5-11] of these were rejected for not meeting inclusion criteria or for being off-topic.

The quality of evidence was rated using an evidence hierarchy for therapeutic, prognostic, diagnostic, and decision modeling. These hierarchies are shown in Appendix III: Rating Evidence Quality. Additional information regarding the hierarchy classification of evidence can be located here: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RECOMMENDATIONS

PICO Question: In myelomeningocele patients with hydrocephalus, does persistent enlargement of the ventricles adversely impact neurocognitive development?

Target Population: Myelomeningocele patients with hydrocephalus.

Recommendation: Currently, there is insufficient data to conclude that ventricular size and morphology impact neurocognitive development.

DISCUSSION

Within the limits of this systematic review, the authors found conflicting Class III evidence[12,13] with regard to the relationship between ventricular size and volume and neurocognitive development and the relationship is currently unknown. More research is needed to better determine the effect of ventricular size and volume on neurocognitive development in children with hydrocephalus from MM.

The impact of ventricular size and morphology on the neurocognitive development of children with MM has received limited attention in the literature until recently. Over the last 10-15 yr 2 trends have emerged that challenge this central dictum of hydrocephalus treatment and place the relationship between ventricular size and cognition at the forefront of hydrocephalus controversy. The first trend is to increase the treatment threshold for placement of a shunt by tolerating larger ventricles and performing more local wound care for CSF leaks following MMC closure.[2,3] The second is the widespread embrace of ETV with CPC as a preferred technique for treatment of hydrocephalus.[4] Both of these approaches spare the child placement of a shunt and thereby prevent downstream chronic shunt problems and morbidity. However, they are also typically associated with persistent ventriculomegaly. At present there exists only limited data to support that these approaches do not threaten normal neurocognitive development.

The most comprehensive study that specifically addresses the issue of ventriculomegaly in hydrocephalic patients with MM was published by Warf et al[12] in 2009. Retrospective analysis of prospectively collected data on a cohort of 93 infants with MMC induced hydrocephalus from Uganda revealed similar neurocognitive outcomes in cohorts of patients treated with ETV/CPC and VP shunt. While follow up and compliance were exceptional, the limitations of the study include retrospective observational cohort design, limited sample numbers, limited follow up time, young age of testing, and lack of longitudinal follow-up. Despite limitations to the power of this study it continues to provide best for available data to address neurocognitive development in cohorts of patients with MM.

In 1992, Fletcher and colleagues reported on cognition and brain white matter changes in a cohort of 23 patients with hydrocephalus.[14] There were 32 hydrocephalic patients studied of whom 17 had open MM as an etiology and 6 had meningocele.

(Continued from previous page)

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Even if the meningocele patients are included as dysraphic then only 72% (23/32) of the cohort has dysraphism and the inclusion criteria for this guideline of 80% is not met. However, this cohort is of substantive size and only marginally misses the inclusion criteria. The authors found no correlation with verbal learning and ventricular size but found significant correlation with both verbal and nonverbal learning with volume loss in the adjacent corpus callosum. Nonverbal learning also correlated with ventricular size in the right but not left lateral ventricle.[1] However, these findings as well as the study overall finding of lower IQ with larger ventricles cannot be included in evidence due to failure to meet the inclusion criteria.

In a related paper, Fletcher et al[6] retrospectively correlated ventricular size and morphology in a cohort of 99 patients with hydrocephalus by utilizing MRI measurements for ventricular size and the Wechsler Intelligence Scale for Children-Revised (WISC-R) validated instrument to measure verbal and performance IQ. This study was excluded because only 40/99 (40%) patients had SB as the etiology of the hydrocephalus. As such it failed to meet inclusion criteria for analysis which required 80% of patients within the cohort have hydrocephalus from MM.

Based on the paucity of data available, there is insufficient evidence to make a recommendation on whether ventriculomegaly adversely affects neurocognitive development in children with MM.

CONCLUSION

The conclusion of this systematic review is that with such incomplete data available the results are mixed from a very limited number of studies and there is insufficient evidence to make a recommendation.

Disclosures

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Conflict of Interest

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Acknowledgments

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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on the Incidence of Tethered Cord Syndrome in Infants With Myelomeningocele With Prenatal Versus Postnatal Repair

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Sponsored by: Congress of Neurological Surgeons (CNS) and the Section on Pediatric Neurosurgery

Endorsed by: The Congress of Neurological Surgeons (CNS), the American Association of Neurological Surgeons (AANS), the Spina Bifida Association (SBA)

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Received, March 25, 2019.
Accepted, May 11, 2019.
Published Online, August 16, 2019.

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BACKGROUND: The incidence of spina bifida (SB) is higher in the developing world as compared to the United States because of folic acid deficiency during pregnancy. Advances in technology have made prenatal repair of myelomeningocele (MM) possible.

OBJECTIVE: The objective of this guideline was to determine if there is a difference in the rate of development of tethered cord syndrome (TCS) in infants who had prenatal closure compared to infants who had MM repair after birth.

METHODS: The Guidelines Task Force developed search terms and strategies to search PubMed and Embase for the relevant literature published between 1966 and September 2016. Strict inclusion/exclusion criteria were used. Full text articles were reviewed and, when appropriate, included as evidence.

RESULTS: A total of 261 abstracts were reviewed. Fifty-four full-text articles were selected for further analysis. Three studies met inclusion criteria.

CONCLUSION: There was Class II evidence from 1 study and Class III evidence from another 2 studies demonstrating that TCS develops in infants with prenatal MM closure at an equal or higher rate than with postnatal closure. There was an increased risk of development of inclusion cysts in infants who underwent in utero closure. Continued surveillance for TCS and/or the development of inclusion cysts in children with prenatal and postnatal closure of MM is indicated (Level II). Differences between prenatal and postnatal repair with respect to the development of TCS and/or inclusion cysts should be considered alongside other relevant maternal and fetal outcomes when deciding upon a preferred method for MM closure.

The full guideline can be found at https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-6.

KEY WORDS: Fetal, In utero closure, Myelomeningocele, Postnatal, Spina bifida, Tethered cord syndrome

Neurosurgery 85:E417–E419, 2019 DOI:10.1093/neuros/nyz266 www.neurosurgery-online.com

The incidence of SB in developing countries is high and under-reported, as compared to that in the United States, due to the limitations of data collection, malnutrition, and folic acid deficiency.[1-3] This systematic review was conducted to evaluate available evidence and to determine the best options for management of patients with MM. The objective of this guideline was to search the current literature, evaluate the evidence, and make appropriate recommendations for clinical management of infants with MM closed prenatally vs postnatally, specifically in reference to the incidence of TCS.

ABBREVIATIONS: COI, conflict of interest; **HC,** hydrocephalus; **JAMA,** Journal of the American Medical Association; **MOMS,** Management of Myelomeningocele Study; **MM,** myelomeningocele; **NEJM,** New England Journal of Medicine; **SB,** spina bifida; **TCS,** tethered cord syndrome

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METHODS

The Guidelines Task Force initiated a systematic review of the literature and evidence-based guideline relevant to the diagnosis and treatment of patients with MM. Additional information about the methods utilized in this systematic review is provided in the introduction and methodology chapter https://www.cns.org/guidelines/guidelines-spina-bifida-chapter-1.

Literature Search

The Guidelines Task Force worked with a research librarian to develop search strategies for relevant the literature published between 1966 and September 2016 in PubMed and Embase. About 261 abstracts screened and of the 54 articles selected, 50 were rejected for not meeting inclusion criteria or for being off-topic and 1 was rejected for including the same patients as a subsequent study. There were 3 studies that met inclusion criteria (see Appendix IV).[4-6] See PRISMA Article Flow Chart in Appendix II.

Rating and Classification of the Quality of Evidence

Demonstrating the highest degree of clinical certainty, Class I evidence is used to support recommendations of the strongest type, defined as Level I recommendations. Level II recommendations reflect a moderate degree of clinical certainty and are supported by Class II evidence. Level III recommendations denote clinical uncertainty supported by Class III evidence. Additional information regarding the hierarchy classification of evidence is found on the CNS Guidelines Procedures and Policies page at: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RECOMMENDATIONS

1. Continued surveillance for tethered cord syndrome and/or the development of inclusion cysts in children with prenatal and postnatal closure of myelomeningocele is indicated (Level II) as there is evidence that prenatal closure may increase the risk of recurrent tethered cord over the baseline rate seen with postnatal closure.

CONCLUSION

There is Class II and III evidence indicating the same or a slightly higher rate of TCS and/or inclusion cyst development in children who had in utero closure of their MM. Additionally, TCS seems to develop at an earlier age in such infants. Increased surveillance for TCS and/or inclusion cysts is therefore warranted.

Disclosures

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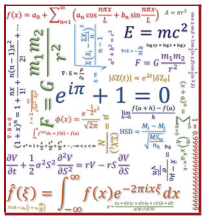
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Acknowledgments

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Fundamentals of Clinical Prediction Modeling for the Neurosurgeon

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Received, November 22, 2018.
Accepted, May 26, 2019.
Published Online, August 16, 2019.

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Clinical prediction models in neurosurgery are increasingly reported. These models aim to provide an evidence-based approach to the estimation of the probability of a neurosurgical outcome by combining 2 or more prognostic variables. Model development and model reporting are often suboptimal. A basic understanding of the methodology of clinical prediction modeling is needed when interpreting these models. We address basic statistical background, 7 modeling steps, and requirements of these models such that they may fulfill their potential for major impact for our daily clinical practice and for future scientific work.

KEY WORDS: Aneurysmal subarachnoid hemorrhage, Clinical prediction, Model development, Neurosurgery, Outcome, Risk assessment

Neurosurgery 85:302–311, 2019 DOI:10.1093/neuros/nyz282 www.neurosurgery-online.com

Clinical prediction models—also called prediction rules, risk scores, prognostic index, or prognostic models—aim to predict the presence of disease (diagnosis) or a specific outcome in the future (prognosis).[1] These statistical models are commonly based on a combination of multiple predictor variables rather than on a single predictor variable or test.[1,2] These models may serve as evidence-based tools needed for medical decision-making and shared decision-making purposes such as counseling patients and their relatives, and have potential in improving scientific research too.[3]

Clinical prediction models have gained popularity in the neurosurgical literature over the years. In the last 2 decades, publications reporting on neurosurgical clinical prediction models have increased exponentially, for a range of clinical outcomes including mortality, surgical complications/side effects, unfavorable functional outcome, psychological outcome, and psychiatric outcomes (Figure 1).

ABBREVIATIONS: aSAH, aneurysmal subarachnoid hemorrhage; **AUC,** area under the receiver operating characteristic curve; **BMI,** body mass index; **CT,** computed tomography; **HR,** hazard ratio; **ICP,** intracranial pressure; **LASSO,** least absolute shrinkage and selection operator; **MAR,** missing at random; **MCAR,** missing completely at random; **MNAR,** missing not at random; **PMLE,** penalized maximum likelihood estimation; **PROM,** patient-reported outcome measure; **SF-36,** Short Form Health Survey; **TRIPOD,** Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; **WFNS,** World Federation of Neurological Surgeons Grading System

Inadequate (statistical) methodology and/or inadequate reporting of the results have led to a reluctance towards application of these models in individual patients or for policy making.[4,5] For example, clinical prediction models for aneurysmal subarachnoid hemorrhage (aSAH) are rarely used based on statistical-methodological concerns.[6] Furthermore, model intercepts are rarely reported which makes risk assessment for new individual patients infeasible. However, good prediction models can be of paramount importance. For example, in stroke patients, the clinical intuition of neurosurgeons and other neuroclinicians may be imperfect and can be outperformed by prediction tools.[7,8]

Nowadays, as we have the responsibility to clearly clarify reports on clinical prediction models to individual patients and their relatives so that they understand their risk, it is of utmost importance to understand the terminology and the fundamentals of this methodology to adequately interpret these models, and to make informed assessments for their potential application in clinical practice and research. However, an oversight that facilitates the neurosurgeon is lacking. The present manuscript aims to be an overview of the fundamentals of

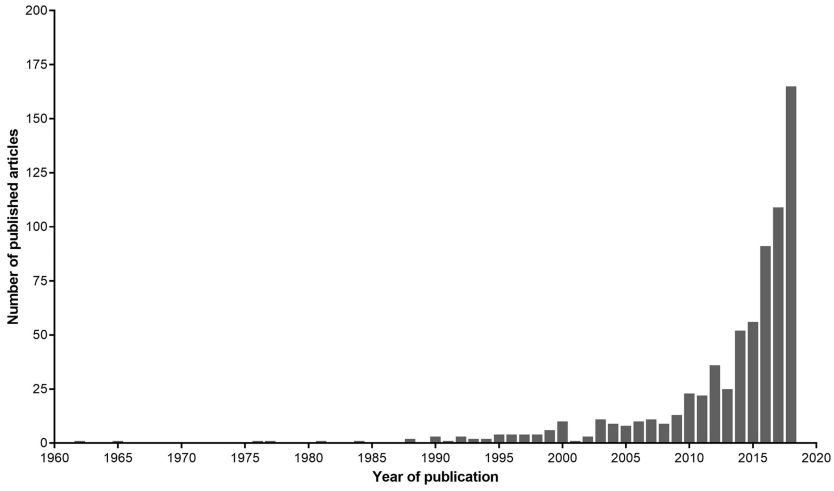


FIGURE 1. *Time trends of the published number of neurosurgical articles reporting on clinical predictions models according to the following systematic search in PubMed until 01.01.2019: (Prognostic-index* OR Prognostic-rule* OR Prognostic-model* OR prediction-index* OR prediction-rule* OR prediction-model* OR predictive-index* OR predictive-rule* OR predictive-model*) AND (Neurosurgery[mh] OR Neurosurgical Procedures[mh] OR Neurosurg* OR Neurological-surg*)*

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clinical prediction modeling for neurosurgeons. We discuss 7 modeling steps for developing robust clinical prediction models with regression analysis.[3,9] We use examples from the field of aSAH.

STATISTICAL FUNDAMENTALS

We first discuss the outcome that is predicted by the model. From a disease-centered perspective, clinician-reported outcomes are preferred and include normally hard endpoints such as mortality and shunt-dependency. From a patient-centered perspective, patient-reported outcome measures (PROMs) are desired such as (long-term) quality of life after aSAH.[10] It is expected that (specific) PROMs in neurosurgery will have a more prominent role in the future.[11]

Continuous Outcomes

For outcomes with a continuous nature such as most psychological outcomes and most PROMs, predictions may come from a linear regression model:

$$y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k + \varepsilon \quad (1)$$

For individual patient risk prediction, the error term ε is omitted:

$$y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k \quad (2)$$

In this model, y is the predicted outcome variable or dependent variable, eg, the Stroke Specific Quality of Life Scale or the Short Form Health Survey (SF-36).[10,12] The predicted outcome, which can be denoted as $\hat{y}$, is the expected outcome for a patient that can be calculated when the α and βs are known. The intercept α is a constant of the model. The intercept equals the predicted outcome for a patient with each x coded 0. If we subtract the mean of each x variable, the prediction is for a patient with mean values of the predictors. Each β expresses the effect on the outcome per 1-unit change in the corresponding predictor variable while keeping the other predictor variables constant. Thus, if in a model for SF-36 the β is 3 for body weight, we conclude that an increase of 1 kg in body weight results in an estimated increase of 3 points in mean SF-36, holding other factors constant. Synonyms for x include independent variable, explanatory variable, covariate, predictor variable, and prognostic factor. These x variables are often incorrectly labeled as parameters in the literature. Variables include quantities that may differ between individual patients.[13] For example, the values of intracranial pressure (ICP), systolic blood pressure and age will vary among patients with aSAH. By contrast, parameters α and β are not direct measurements from patients but are estimates from a statistical model based on a sample of patients.[13] The middle part of the model (ie, $\alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$) is known as the linear predictor (lp). The error ε in equation 1 is termed the residual and reflects the difference between the observed y and the predicted y.

Binary Outcomes

Commonly, we want to predict neurosurgical outcomes that are binary, eg, mortality or shunt-dependency following aSAH.

It is convenient to analyze the outcome in terms of probability, rather than directly, to bound the predictions between 0 and 1. It is common to model the log odds as a linear function of the predictors—ie, the logistic regression model:

$$\ln \frac{p}{1-p} = \text{logit}\,(p) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k \quad (3)$$

The probability of one outcome (eg, "yes" for shunt-dependency) is given by p. The probability of the other outcome ("no") is then $1 - p$. The outcome is again linked to a linear combination of a set predictor variables. The β represents the change in the logit corresponding to a change of one unit in the predictor variable.[14] For a better understanding of the regression coefficient, the odds ratio is often used: e^{β},[14] which tells us how much the odds of achieving a positive outcome changes when corresponding variable x changes by one unit.

The inverse of the logit (ie, the logistic function, equation 4) is useful for individual patient absolute risk prediction (p):

$$p = \frac{1}{1 + e^{-(\alpha+\beta_1 x_1+\beta_2 x_2+\cdots+\beta_k x_k)}} \quad (4)$$

We note that e^{lp} equals the odds of the outcome. When lp is zero, the probability is exactly 50%.

When we however have to deal with an outcome that includes 3 or more categories, extensions of the standard logistic regression model are available for polytomous risk prediction.[15] For unordered and ordered outcome categories, the multinomial and ordinal logistic regression model can be used, respectively. Furthermore, if the number of ordered categories is sufficiently large—ie, at least 5 values as a rule of thumb—linear regression as depicted in Equation 1 could be applied.

Time-to-Event Outcomes

When the outcome of interest is time until an event occurs, survival prediction models are usually applied. These models take the time between a starting point such as surgical clipping of an aneurysm and the endpoint such as death into account.[16] The follow-up of the included patients is often incomplete: some may have been followed for 1 yr, some for 2 yr not having experienced the endpoint while in the study, while we, for example, are interested in estimates of 5-yr survival.[3] Consequently, for some patients, the survival time will be unknown and these observations are censored. Censoring makes survival models unique. To analyze survival data, the Cox proportional hazard model is generally used,[17] which is typically depicted as:

$$h(t) = h_0(t) \times e^{(\beta_1 x_1+\beta_2 x_2+\cdots+\beta_k x_k)} \quad (5)$$

The Cox model assumes proportionality of the hazard ratios (HRs).[3] The proportionality assumption is that the HRs are constant on the multiplicative scale over time, regardless of the baseline hazard. The statistical distribution of the baseline hazard, which functions as an intercept that varies with time,[16] is left unspecified in the Cox model. Hence, the Cox model is semiparametric. It enforces no constraints on the statistical distribution of the hazard.[3,18]

To predict survival of an individual patient, the survival function $S(t)$ is normally used:

$$S(t) = S_0(t)^{e^{(\beta_1 x_1+\beta_2 x_2+\cdots+\beta_k x_k)}} \quad (6)$$

Here, the β estimates from the fitted Cox model (equation 5) are combined with a nonparametric estimate of the baseline survival ($S_0(t)$) to estimate the predicted survival at time t given a set of predictors. The baseline survival can be derived from the Cox model.[3] Alternative approaches for analyzing survival data are available. For example, parametric models can be chosen which make some assumptions on the statistical distribution of the baseline hazard. One example is the Weibull model, which is attractive to make stable predictions at the end of follow-up.[3] Furthermore, extrapolation becomes feasible because of the parametric nature.[3]

MODEL DEVELOPMENT

Prior to the start of designing a new prognostic model, one should question the need for a new model. Updating of existing models may be more useful; at least existing models should be searched for. If a new prognostic model is desired, the model objective should be clearly stated. Importantly, a model may aim to provide predictions vs give insight in the relevance among predictors.[19] These aims have implications for the steps of model development. Below, a practical systematic strategy is presented that may help to develop robust und transparent models.[3] Table 1 shows a summary of the model development process.

Step 1—Description of Patient Data

The empirical data used should adequately represent the neurosurgical population of interest at that time and geographic location. As neurosurgery is continuously progressing, historical data may be inappropriate. Furthermore, data are often primarily collected for other research aims and selection of patients may limit the usefulness of the resulting model. Therefore, an appropriate description of the study design is warranted.

Study Design

Cohort studies are preferred in clinical prediction studies rather than case-control studies and cross-sectional studies.[20] A cohort describes a group of patients which share a single defining event and so becomes permanent.[21] Retrospective cohort studies are most often used, as they are often cheaper and faster to conduct. However, selection of patients and variables is then done in retrospect and is therefore prone to selection bias. In prospective cohort studies, the variables of interest are assessed prospectively and pre-defined by protocol reducing the risk of selection

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TABLE 1. Summary Table of 7 Steps for Developing and Evaluating Neurosurgical Clinical Prediction Models

Theoretical steps	Practical checks	Comments
Step 1—Description of patient data	Study design	Prospective or retrospective? Evaluate inclusion and exclusion criteria when an existing data set is used.
	Variable selection	Identify candidate predictor variables by subject matter knowledge and literature review.
	Sample size	Be careful with rules of thumb such as at least 10 EPV. For sample size calculation, it is recommended to take overfitting and the estimation of the overall outcome risk into account.
Step 2—Data preparation	Coding of variables	Consider coding of categorical variables carefully. Avoid dichotomization of continuous predictor variables.
	Missing data	Consider modern imputation techniques. Complete case analysis as sensitivity analysis.
Step 3—Model specification	Selection of variables	Be careful with stepwise selection procedures. High *P*-values that are used for stopping in large data sets seems to be safe. Subject matter knowledge is vital.
	Assessment of model assumptions	Evaluation can be performed by statistical tests. Consulting a statistical expert is recommended.
Step 4—Model estimation	Estimation method of the model parameters; shrinkage methods applied?	Consider modern estimation techniques to minimize overfitting.
Step 5—Model performance	Overall, calibration, and discrimination indices	Evaluate overall performance (explained variance, R^2) and ABCD: calibration (graphically, with parameters $\underline{\alpha}$ for baseline risk, and $\underline{\beta}$ for calibration slope), discrimination ($\underline{c}$-statistic) and $\underline{d}$ecision analytic measures if the model is for decision support.
Step 6—Model validation	Internal validity	A prerequisite. Bootstrap validation or cross-validation is recommended.
	External validity	Claims on transportability require multiple validation studies which may show variability in performance, related to the selection of patients, definition issues, and poor model fit. Local updating may be required, especially for the baseline risk.
Step 7—Model presentation	Mathematical model methodology	Present final raw regression formula. Adhere to the TRIPOD checklist for transparent reporting.

EPV, events per variable.

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bias. Randomized controlled trials are often used due to the high quality of the data and large sample size. For such data, adjusting for the studied treatment in the clinical prediction model needs to be considered.[22] Moreover, the generalizability may be questionable as a result of specific selection criteria.[22]

Candidate Predictors

In our field—as in other fields—we often have to deal with relatively small data sets although many candidate prognostic variables are of interest and available. Prior to the start of the study, stringent identification of the candidate prognostic variables is pivotal for reliable model development. Candidate prognostic variables should be ideally clearly defined, easily accessible, and being measurable with minimal measurement error.[23,24] Subject matter knowledge and thorough review of the literature is crucial to reduce the number of prognostic variables.

Sample Size

To achieve a relevant model, the patient sample drawn from the population of interest should be representative and of adequate size. An adequate sample size should ensure that the number of patients is large enough relative to the model complexity, considering the number of considered predictor parameters, potential transformations, and statistical interaction terms.[25,26] In the case of binary and time-to-event outcomes, the number of patients with the event is most relevant. The number of events is the dominant factor if the events are relatively infrequent, such as occurring in <20% of the patients. Larger sample sizes imply more stable model results, eg, accurate estimates of the parameters and more realistic performance measures of the prediction model. If many prognostic variables are considered, the model results may mislead us as looking promising even when all prognostic variables are noise.[27] Spurious findings may emerge that may look important in one data set but are not replicable in other sets of patients: "overfitting."[3,27] The rule of thumb of 10 events per

variable has generally been accepted as a minimum. Recently, Riley et al[25,26] proposed a more refined approach to define an adequate sample size. Calculations should be based on the number of patients, the number of events (in case of binary and time-to-event outcomes), the number of predictor parameters, the anticipated strength of the prognostic effects, the maximum allowed amount of overfitting, and the desired precision in estimation of the overall outcome risk.[25,26] One should note that categorical variables with more than 2 categories such as World Federation of Neurological Surgeons Grading System (WFNS) and Fischer grades may have more predictor parameters (degrees of freedom). Assessments of overfitting and validated model performance are essential unless the sample size was huge and the number of predictors small (eg, 3000 events, 20 predictors, EPV>100).[28]

Step 2—Data Preparation

Coding of Variables

Several options are available to code the variables of interest for the statistical analysis. Categorical variables can be fused for simplicity and for sample size matters. We should be cautious with dichotomizing continuous predictor variables. For example, it is unlikely that the prognosis of patients with a body mass index (BMI) of 29.9 will differ from those with a BMI of 30.1.[29] Generally, a continuous prognostic variable is better handled as a linear term in the statistical model. The assumption is then, for example, that the effect of a 5 mmHg increase in ICP is than the same at an ICP level of 10 mmHg or 20 mmHg for intensive care patients with aSAH. If a nonlinear function is expected, flexible transformations can be examined.[3]

Missing Data

Data sets are often incomplete. Generally, missing data mechanisms are grouped as missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). MCAR is not related to observed or missing data; eg, computed tomography (CT) scans might be missing due to occasional malfunction. MAR relates to other observed data meaning that the missing values can be estimated by the relationships observed in the data set. For example, if CT scans are more often missing in younger patients, MAR will hold if patient age is modeled. MNAR relates to the missing data itself or on other unobserved predictors. Thus, the missing values are not covered by the relationships observed in the data set. For example, CT scans are missing due to a severe clinical condition status which is not accessible in the data set.[3] Missing data can be addressed in several ways. First, a complete case analysis can be done. Here the researcher deletes all subjects with missing data from the data set before carrying out the statistical analysis. The risk of reducing the sample size is the potential bias in the model results because the missing data may not be at random. Complete case analysis can be considered reasonable when missingness is low (say <5%).[30] Second, imputation methods can be used to produce the estimates of the missing values and hence gain statistical power for prediction.[3] Among the imputation methods, multiple imputation is generally preferred. This assumes an MAR mechanism.[3,31,32] Subject matter knowledge is of prominent importance in judging how data went missing since MAR is an untestable assumption and MNAR hence always remains open.[3] One might question imputation especially when the fraction of missing data is substantial. Another consideration is whether data will be frequently missing in the clinical setting where the model may be applied; it may then be wise to consider submodels.[33] Neurosurgeons who have to deal with a missing predictor variable while deploying a prediction model cannot simply ignore this predictor as this will create invalid results.[34] Among the techniques that aim to account for missing data when deploying the prediction model in daily practice, multiple imputation is possible making the application of the prediction model more complex.[34] Alternatively, submodels may be applied.[33] Thus, missing data should ideally be kept to a minimum since each solution strategy has constraints.

Step 3—Model Specification

Selection of Variables

In the neurosurgical clinical routine, a clinical prediction model commonly has to be simple to apply. Parsimonious models that hold most of the prognostic information are desired. For simplification of a prediction model, stepwise selection is often used and traditionally includes, amongst others, 2 main variants[3]: (1) simultaneous entry, meaning that all prognostic variables are entered in the model at once, followed by stepwise elimination (backward selection); and (2) sequential entry, meaning that the prognostic variables are entered in the model in forward steps. Stepwise selection is automatically executed by a computer and is typically guided by statistical rules, eg, with the standard significance level 0.05 for inclusion of predictors. Furthermore, common stopping rules are the Akaike Information Criterion (effectively a higher *P*-value for selection) and Bayesian Information Criterion.[3,35] Although still commonly applied, automated stepwise selection is criticized as it leads to bias of the model results, especially in smaller data sets.[36,37] Stronger, it was a reason for rejecting manuscripts.[38] A promising alternative to data-based selection of variables is to apply shrinkage or penalization methods (discussed in Step 4). Some attain model selection by shrinking regression coefficients to zero such as the least absolute shrinkage and selection operator (LASSO) and elastic net regression.[39] However, the best way is to limit the necessity for data-based selection of variables by using subject matter knowledge.[40]

Assessment of Model Assumptions

When multivariable models are used for clinical prediction modeling, the underlying assumptions should be considered. These include, but are not limited to, the linearity of continuous predictors and the additivity assumption. Mathematical transformations of the data can help to make these assumptions

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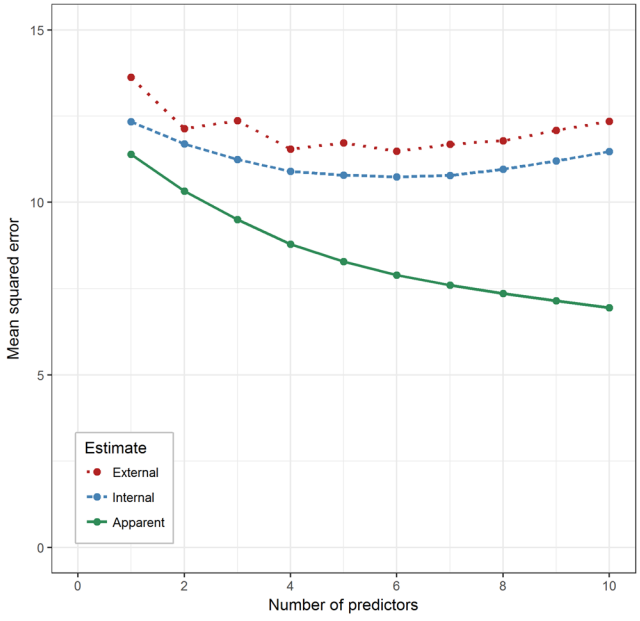


FIGURE 2. *Estimated performance for a linear regression model (mean squared error, means of 1000 simulations). Predictions were generated with 10 predictors with decreasing strength in samples of 50 patients. The apparent performance improves (less error) with increasing numbers of predictors. The validated performance worsens after an optimum at 6 predictors. Internal performance refers to samples of similar patients, while external performance refers to performance in a setting with slightly different effects of the 10 predictors.*

more plausible. For example, the additivity assumption—ie, the regression formula implies additivity of effects—can be checked with statistical interaction terms. Interaction means that the effect of a prognostic variable depends on a second prognostic variable. Addressing violations may lead to a model that describes the underlying data well. However, at the same time the overfitting may increase, ie, the model performs worse in new sets of patients and is not generalizable.[3] A less complicated (parsimonious) model that describes the data under study in a suboptimal way can have a higher predictive performance in new patients.[19] This principle is illustrated in Figure 2. We note that there are limits to the ability of regression models, and consulting a statistical expert is recommended for this step. In small data sets, relying on some assumptions may be the most sensible approach rather than testing model variants and choosing an apparently best but overfitted model.

Step 4—Model Estimation

The next step is to estimate the model parameters. For linear regression models, the model parameters are generally assessed with the method of ordinary least squares so that the mean squared residual error is as small as possible. For logistic or Cox regression models, maximum likelihood methods are generally used.[40] The parameter estimates derived from these model estimation techniques may be too extreme for predictive purposes, especially in small data sets, as the predictor–outcome associations and the data idiosyncrasies are captured in the model estimation.[41] This overfitting results in exaggerated predictions for new patients. To ameliorate predictions from such a regression model, shrinkage methods can be used to shrink the regression coefficients towards zero.[3] Common shrinkage methods include uniform (or linear) shrinkage, penalized maximum likelihood estimation (PLME, or ridge regression), and the LASSO.[3,39,42] Shrinkage applies to regression coefficients after model estimation. PLME and LASSO directly shrink the parameters during the model estimation using penalized maximum likelihood.[3,39,40] LASSO-estimated parameters can be zero. This is, in effect, the same as excluding the corresponding variables from the model and nicely links model estimation to model specification.

Step 5—Model Performance

Performance indices are needed to check the quality of the prediction model. The performance indices may include an overall model performance measure, such as explained variance (R^2), which ranges from 0 to 100%. R^2 measures the proportion of the variability in the outcome of interest that is explained by the prediction model. Outcome prediction models for aSAH typically have R^2 values under 50%.[43]

Measures for calibration and discrimination are essential. Discrimination tells us how good the constructed prediction model distinguishes events from nonevents. The *c*-statistic calculates the probability that the prediction model provides a higher score for a randomly selected patient with the outcome compared to a randomly patient without the outcome.[44] The *c*-statistic is equivalent to the area under the receiver operating characteristic curve (AUC). AUC equals 0.5 in case of no discriminative ability, thus an uninformative model. A perfect model will give a perfect discrimination which will be reflected in a *c*-statistic equaling 1.0. Variants are available for polytomous outcomes (outcomes with more than 2 categories) and time-to-event outcomes, eg, the ordinal *c*-index, Harrell's *c*-index, and Royston's D statistic.[40,45-47]

Calibration is related to the agreement between the predictions of the model with the observed outcomes of the data that can be well evaluated graphically by a calibration plot. For models with continuous outcomes, the calibration plot is a scatter plot with the predictions on the x-axis and the outcome on the y-axis. For models with binary outcomes, as the outcome has only 0 and 1 values, smoothing techniques are needed to estimate the observed probability (y-axis) in relation to the predicted probability (x-axis).[48] To illustrate, Figure 3 shows 2 hypothetical calibration plots for chronic shunt-dependency after aSAH. The 45° line ($\alpha = 0$ and $\beta = 1$) in the calibration plot is the line of identity for a perfectly calibrated prediction model. Figure 3A shows a relatively well-calibrated hypothetical model suggesting the predicted risks are reliable, especially in low-risk patients. The red curve in

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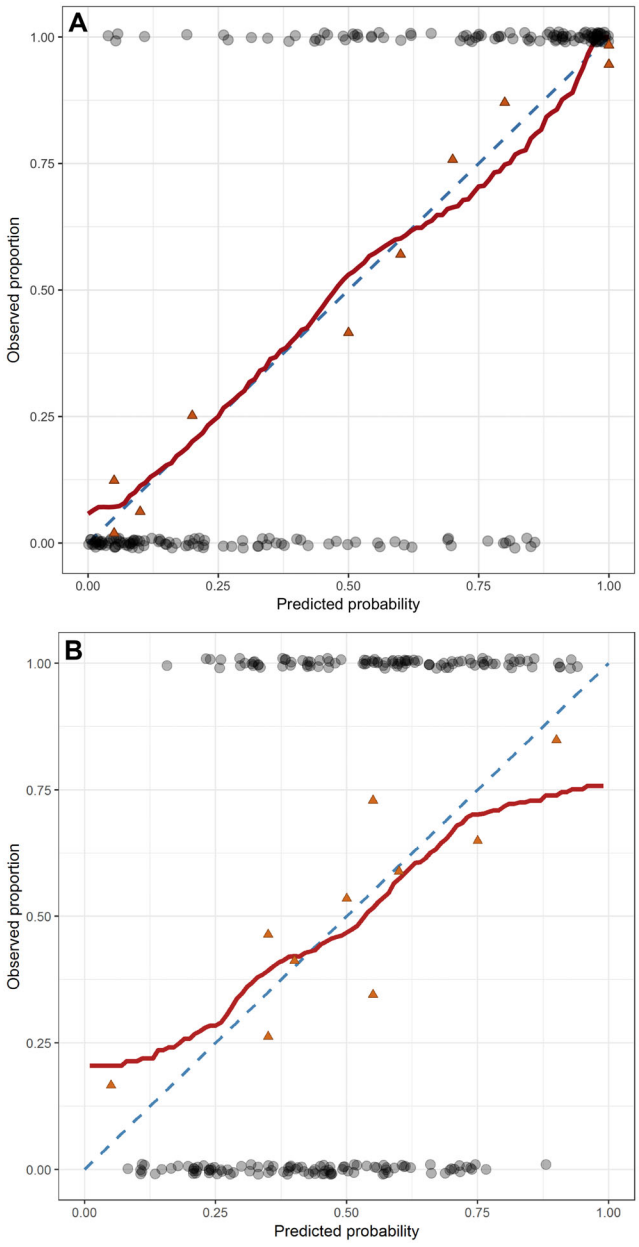


FIGURE 3. *Two calibration plots showing the predicted probability against the observed proportion. The distribution of the outcome observations is depicted as thick gray dots at the bottom and at the top of the chart. The ideal line (dashed blue line) is the 45-degree straight line that corresponds to the line of perfect calibration. The red line shows the estimated probability. The actual outcome by deciles of risk is shown by the amber triangles.* **A** *shows a relatively well-calibrated model.* **B** *shows a relatively poor calibrated model.*

Figure 3B suggests an underestimation in low-risk patients and an overestimation in high-risk patients. This phenomenon is typically seen in overfitted models.[41] Statistical tests are available to assess model calibration such as the Hosmer–Lemeshow test. However, this test is not recommended, since it merely provides a *P*-value rather than an insightful assessment of calibration.[3,48] At external validation, the calibration-in-the-large statistic and the calibration slope are highly recommended in the performance assessment of the prediction model.[49]

Step 6—Model Validation

It is of utmost importance to check the validity of the constructed model for new neurosurgical patients. Model validation can be divided into internal and external validation. Internal validation refers to the reproducibility of the model, while external validation refers to the transportability (or generalizability) of the constructed model.[50] Validation of model predictions is critical to gauge the usefulness of the model.

Internal Validation

Internal validation is a minimum requirement for every clinical prediction model.[1] It is known that a model is likely to perform worse on new patients than on the sample used for its generation—the apparent performance measures of the model are overestimated. This statistical phenomenon is known as optimism.[51] Optimism is the difference between apparent model performance and true model performance.[3] The true performance refers to the model performance in the underlying population, whereas apparent performance refers to the model performance in the study sample where the model was derived from.[3] Internal validation techniques aim to quantify any optimism in model predictions, specifically whether low predictions are too low and high predictions too high. Useful techniques include cross-validation or bootstrap validation. These reuse the data set on which the model was generated.[52] Bootstrapping is generally most efficient. A bootstrap sample is an impression of the original data set and is created using random sampling of patients with replacement from the original data set.[41] Thus, patients can be selected multiple times. Bootstrap samples are of the same size as the original data set.[3] To estimate model optimism, a prediction model is created in each bootstrap sample, and the model performance is evaluated in the bootstrap sample and the original sample accordingly.[3] Usually, a large number of bootstraps—eg, 500 bootstraps—are executed to reveal a proper impression of the model optimism.

External Validation

The next vital step is assessing the performance of the developed model in an external data set. External validation addresses the question whether the model is applicable to a different setting. Examples of a different setting include another hospital (eg, academic vs non-academic hospitals), another patient selection (eg, low-grade vs high-grade aSAH patients), and another treatment selection (eg, endovascular treatment

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TABLE 2. Logistic Regression Model for 30-d Chronic Shunt-Dependency After aSAH Based on Hypothetical Data

Predictor variable	OR (95% CI)	*P*-value
Age (years)	1.04 (1.01-1.08)	.02
Sex (male vs female)	0.87 (0.36-2.11)	.76
Fisher (low vs high)	1.52 (0.55-4.21)	.42
WFNS (low vs high)	2.38 (0.76-7.39)	.14
Treatment (clipping vs coiling)	3.76 (1.44-9.83)	.01

aSAH: aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons Grading System; OR: odds ratio; CI: confidence interval.

The regression formula is: $\ln(p(\text{shunt-dependency})/(1- p(\text{shunt-dependency})) = -3.33 + 0.04^{*}\text{age (in years)} + -0.14^{*}\text{sex (0 = female, 1 = male)} + 0.42^{*}\text{Fisher (0 = Fisher I or II (low), 1 = III or IV (high)} + 0.87^{*}\text{WFNS (0 = WFNS I, II, or III (low), 1 = IV or V (high)} + 1.33^{*}\text{Treatment (0 = coiling, 1 = clipping).}$

vs surgical treatment). External validation studies may show variability in performance across settings. If identified, we should aim to find explanations for such heterogeneity in performance.

Step 7—Model Presentation

The presentation of the final model should be adequate and sufficiently precise to allow the reader to apply the model properly. The model allows us to make predictions for future patients and provides estimates of the importance of the prognostic variables used. The presentation of the final model should adhere to the research question being addressed. If future prognostication—ie, using the model for the calculation of the probability of the outcome in new patients—is aimed, the mathematical formula including the intercept with the raw regression coefficients of the final prediction model is needed (as in Table 2). The coding for categorical prognostic variables and the units or scales of the continuous prognostic variables should be presented. Next to the regression formula, other presentation formats exist including score charts and nomograms.[3]

We recommend to use the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement checklist for transparent presentation of a clinical prediction model in a scientific journal.[53]

APPLICATION OF THE PREDICTION MODEL

Clinical Application

Availability of the linear predictor or the prognostic algorithm is a requirement for prognostication. Equations 2, 4 and 6—as presented in the section on Statistical Fundamentals—are commonly used for prognostication. A hypothetical model for 30-d chronic shunt-dependency after aSAH was created to illustrate clinical application. Table 2 shows the output of the logistic regression model, with the formula enabling calculation of the risk for new patients. Following equation 4, the predicted risk for a shunt within 30 d for a 70-yr-old male aSAH patient with a high Fisher and high WFNS score treated with a surgical clipping equals 88%:

$$p = \frac{1}{1 + e^{-(-3.33+(70 \times 0.04)+(1 \times -0.14)+(1 \times 0.42)+(1 \times 0.87)+(1 \times 1.33))}} = 0.88$$

Numerous factors are related with the application of a prediction model in clinical practice.[1] Nowadays, mobile applications are increasingly available for the clinical application of the model. For example, an app was created to make an aSAH prognostic model easily and reliably.[43] The generalizability of a prediction model can be a serious problem.[54] Models developed at a single center may, for example, not be applicable to other geographical locations or different clinical settings. Therefore, external validation and quantification of heterogeneity in performance across a range of clinical settings is vital before applying a model widely.[49] Some updating of the model may be necessary, specifically for the baseline risk estimates.

Scientific Application

As the neurosurgical field is continuously evolving, the performance of a prediction model may wane. It is advised to update known clinical prediction models in future research rather than build new ones when new prognostic variables are of interest.[1] For example, new studies may assess incremental value, ie, analyzing the effect of an additional predictor variable to a known prognostic model. Progress in developing highly effective models will be fastest if researchers update the work of others rather than starting from scratch to develop unique models each time.[55] Next to these options to improve the performance of the model itself, the model can also be used to help other research projects. For example, the developed model can guide the selection of patients in randomized controlled trials and may help to control for confounding in epidemiological studies.[3]

We have thus far focused on clinical prediction models which provide predictions of the outcome of interest, and decision making is left to the user. Future research could be tailored to impact studies—ideally randomized studies[20]—and further evaluation of the prediction model with decision analytic approaches such as the Net Benefit technique.[3,56] The latter extends the prediction model into a decision model using risk thresholds to test whether a clinical decision does more good than harm.[56] These techniques can be very useful for decision making, albeit are not always of direct interest. For example, a prediction model to inform the patient's relatives of the risk of shunt-dependency after aSAH would not need a decision model.

CONCLUDING REMARKS

The present overview should provide a synopsis and introduction for the neurosurgeon and for scientists in the field of neurosurgery on basic issues involved in clinical prediction modeling. The closer a model is to the underlying biology, the better it would be able to bring the field forward, clinically and scientifically. As a model is derived from empirical data from a

set of patients that are drawn from a neurosurgical population, high quality of the empirical data is needed. Furthermore, to learn from the patterns in the underlying population, robust statistical methodology should be applied. Therefore, methodological and statistical guidance is recommended to ferret out predictor–outcome relations for prediction models. With highly careful modeling in one specific data set, the model may not be generalizable to other settings. Specifically, calibration may be the Achilles heel of prediction models.[54] Neurosurgeons should be aware of the fundamentals and limitations when interpreting and applying neurosurgical clinical prediction models. We note that other approaches to model development receive increasing attention. For example, machine learning approaches such as random forest and neural networks are increasingly employed.[57] These approaches rely more on discovery of patterns in the data and use less external subject knowledge. Therefore, they require substantially larger sample sizes to prevent noise discovery and overfitting.[58] Furthermore, machine learning models are more like black boxes and therefore difficult to interpret. We believe that regression models, if used sensibly, will remain a default reference framework for clinical prediction modeling.[54,59]

To conclude, since many steps warrant a combination of clinical subject matter knowledge, methodological and statistical knowledge, it is vital that neurosurgeons collaborate with experts in the field of epidemiology and statistics when developing, validating, or applying clinical prediction models.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Optical Principles of Fluorescence-Guided Brain Tumor Surgery: A Practical Primer for the Neurosurgeon

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Received, November 25, 2017.
Accepted, June 18, 2018.
Published Online, July 30, 2018.

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Fluorescence-guided surgery is a rapidly growing field that has produced some of the most important innovations in surgical oncology in the past decade. These intraoperative imaging technologies provide information distinguishing tumor tissue from normal tissue in real time as the surgery proceeds and without disruption of the workflow. Many of these fluorescent tracers target unique molecular or cellular features of tumors, which offers the opportunity for identifying pathology with high precision to help surgeons achieve their primary objective of a maximal safe resection. As novel fluorophores and fluorescent probes emerge from preclinical development, a practical understanding of the principles of fluorescence remains critical for evaluating the clinical utility of these agents and identifying opportunities for further innovation. In this review, we provide an "in-text glossary" of the fundamental principles of fluorescence with examples of direct applications to fluorescence-guided brain surgery. We offer a detailed discussion of the various advantages and limitations of the most commonly used intraoperative imaging agents, including 5-aminolevulinic acid, indocyanine green, and fluorescein, with a particular focus on the photophysical properties of these specific agents as they provide a framework through which to understand the new agents that are entering clinical trials. To this end, we conclude with a survey of the fluorescent properties of novel agents that are currently undergoing or will soon enter clinical trials for the intraoperative imaging of brain tumors.

KEY WORDS: 5-Aminolevulinic acid, Brain tumor, Fluorescein, Fluorescence-guided surgery, Glioma, Indocyanine green

Neurosurgery 85:312–324, 2019 DOI:10.1093/neuros/nyy315 www.neurosurgery-online.com

Advances in fluorescence imaging over the past half-century have revolutionized the field of biological research. A diverse palette of fluorophores has become an integral part of modern laboratory work, enabling the visualization of biomolecules and cellular processes with high resolution in real time.[1-3] Translating the success of fluorescence imaging from the laboratory to animals and then to human patients in the surgical theater has required bold physician-scientists and courageous patients.

Fluorescence-guided surgery (FGS) relies on the accumulation of an administered fluorescent dye and visualization of the fluorescence signal during surgery (Figure 1). This approach has found particular utility in oncologic surgery, where the exact extent of disease may not be apparent, but a safe maximal resection of tumor tissue is essential.[4] The first attempt to use a fluorescent dye—fluorescein—to identify gliomas was reported in 1948.[5] After early work with fluorescein and indocyanine green (ICG),[6] a major advance was achieved by Stummer and colleagues in Europe in 2006.[7] In a randomized multicenter phase III trial, they found that 5-aminolevulinic acid (5-ALA) guidance led to complete resections nearly 2 times more

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **BBB,** blood-brain barrier; **FGS,** fluorescence-guided surgery; **FRα,** folate receptor alpha; **FRET,** Förster resonance energy transfer; **GBM,** glioblastoma multiforme; **HGG,** high-grade glioma; **ICG,** indocyanine green; **MRI,** magnetic resonance imaging; **NIR,** near infrared; **PPIX,** protoporphyrin IX

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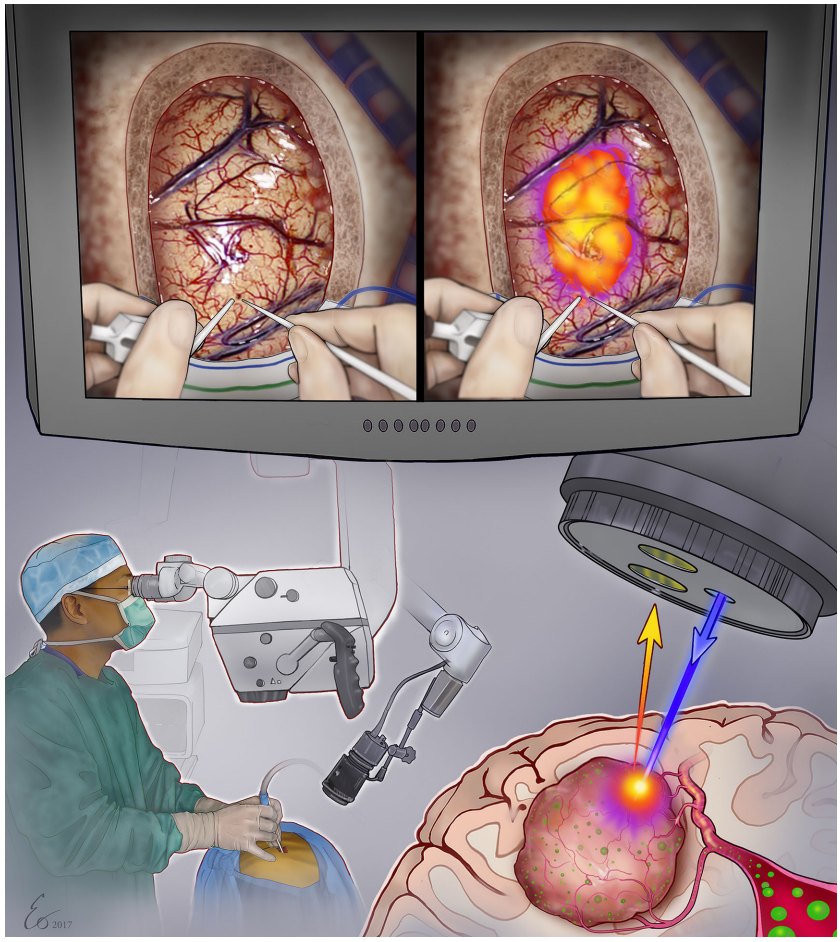


FIGURE 1. *An illustration of fluorescence-guided surgery depicting the surgeon (lower left), the tumor with fluorescent tracer accumulation (lower right), and a video screen showing the view from the operating microscope with (upper right) and without (upper left) fluorescence guidance. © CHOP, by Eo Trueblood. All rights reserved.*

frequently than standard techniques,[7] and in the decade since, complete resection rates have been reported to be as high as 70 to 90%.[8-10] However, 5-ALA guidance is largely limited to high-grade gliomas (HGGs) due to poor or inconsistent fluorescence signals observed in lower grade gliomas and other brain tumors types.[11,12] Recently, the FDA approved the use of 5-ALA for the intraoperative visualization of HGGs during brain tumor surgery. Worldwide, primarily outside of the USA, thousands of patients have undergone 5-ALA guided resection of brain tumors, and there is increasing evidence that 5-ALA guided surgery yields improved outcomes.[12-16]

5-ALA is the first of likely many other fluorescent tracers that will soon become a regular part of the neurosurgeon's toolbox. Numerous clinical trials are ongoing with innovative imaging agents, and even more are under development in the preclinical stage.[17,18] Many of these tracers combine tumor-targeting moieties and novel fluorophores to increase the tumor signal over the background signal from normal tissue, and also to visualize tumors that are lower grade, smaller, or deeper within the brain. These agents may also be used in combination or independently with intraoperative magnetic resonance imaging (MRI) and ultrasound to improve tumor localization.

Given the recent surge of interest and activity within this field, we present here a primer on the optical principles of fluorescence, with a focus on basic and advanced concepts directly relevant to the neurosurgeon in the operating room and in the research laboratory. These principles offer insight into the critical properties of novel tracers under development and the selection of the most promising candidates for further research and clinical testing. In practice, they will help understand the limitations of existing technologies, troubleshoot certain intraoperative issues, interpret fluorescence signals during procedures,

and select optimal instrumentation.[19,20] These basic science concepts will also support a common language with the scientists and engineers who develop novel fluorescence tracers, and from this dialog, neurosurgeon-investigators may continue to offer constructive and granular insight into areas that are most in need of innovation. The advancement of FGS is an interdisciplinary effort, and we envision neurosurgeons as leaders in bringing these new technologies from the laboratory bench into routine operative practice.

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OPTICAL AND PHYSICAL PRINCIPLES OF FLUORESCENCE

In this section, we will use 5-ALA, ICG, and fluorescein as specific examples to illustrate how the principles of fluorescence directly inform FGS. We focus on these 3 agents because they are FDA approved molecules, commonly used tracers in the neurosurgical literature, and representative members of important classes of fluorescent molecules that neurosurgeons may encounter in preclinical studies, clinical trials, and operative use.

FGS is fundamentally based on the detection of light produced by a fluorescent molecule—a fluorophore—that accumulates within a tumor. This method for identifying tumor tissue is distinct from leveraging tactile differences, applying image registration technologies, and even the millennia-old practice of using sun-, candle-, or LED light, and relying on the reflectance of light off of different tissues to demonstrate anatomic features. Thus, we will begin our review here, with a discussion of light absorbance and reflectance, which we will then contrast with fluorescence and illustrate the unique advantages of FGS.

Basic Mechanisms of Light Absorbance and Reflectance

When any object is illuminated by white light, which includes all wavelengths of the visible spectrum (400-700 nm), the object will absorb certain wavelengths of light and reflect back others (Figure 2A). The reflected wavelengths correspond to the perceived color. The most commonly used light source in the operating room is white light from overhead or from a light box. Upon illumination of the brain parenchyma, the exposed tissue may be perceived as yellow. This is due to the inherent property of brain tissue to absorb violet-blue light and reflect yellow light. If a tissue is stained with methylene blue, upon white light illumination, red light (600-700 nm) is absorbed, and the remaining wavelengths of light are reflected, detected by the eye, and interpreted as blue.

The mechanism of absorption is best illustrated using a simplified Jablonski diagram (Figure 2B). Upon exposure to light, the absorbing molecule, or chromophore, is excited from its ground electronic state (S_0) to an excited electronic state (S_1). The wavelength of light (λ_{abs}) absorbed corresponds to the energy gap between S_0 and S_1, an intrinsic property of the chromophore. The chromophore may then return to the ground state by releasing the energy as heat. For example, chromophores in asphalt are excited to S_1 upon absorption of all wavelengths of light from sunlight. Since nothing is reflected, asphalt is perceived as black. The energy is then released as heat, which is why asphalt feels hot on a sunny day.

Basic Mechanisms of Light Fluorescence

The process of fluorescence begins in the same way: light is absorbed and excites the fluorophore to S_1. However, it decays back to S_0 by releasing a portion of the energy as light, which is detected as fluorescence (Figure 2B). For example, protoporphyrin IX (PPIX), the fluorophore generated by endogenous catabolism of 5-ALA, first absorbs the excitation blue light and then releases a portion of the energy as emitted red light. Notably, infrared radiation of a longer wavelength can be a form of heat, which may limit its use. Overall, many fluorophore-intrinsic and local environmental factors influence the intensity of the detected fluorescence signal (Figure 2C), and these factors are discussed herein as they pertain to fluorescence-guided neurosurgery.

Stokes Shift

The Stokes shift is the difference between the wavelengths of maximal light absorption (λ_{abs}) and emission (λ_{em}; Figure 3A). Most fluorophores emit longer wavelength light than they absorb.

The underlying mechanism (Figure 3B) involves a quantum mechanical effect. The S_0 and S_1 states have different optimal molecular geometries (eg, bond lengths). When the fluorophore is excited from S_0 to S_1, it arrives with a molecular geometry that was optimal for S_0, but is now suboptimal for S_1. Relaxation of the molecular geometry to the optimal arrangement for S_1 releases energy as heat. Similarly, after the excited fluorophore emits light as fluorescence and returns to S_0, it arrives with a suboptimal geometry for S_0 and undergoes relaxation to the optimal arrangement for S_0 with concomitant release of energy as heat. In total, the initially absorbed energy is released in part by heat and in part by light, leading to emission of lower energy and longer wavelength light.

In practical terms, the Stokes shift allows for selective detection of emitted light without interference from reflected or scattered light from the excitation beam. Excitation and emission filter sets are selected for a particular fluorophore to maximize its signal-to-noise ratio. Stokes shifts are typically 10 to 30 nm; however, some, such as that of PPIX, can be as large as 220 nm (Figure 3).[18] Thus, although fluorescein and 5-ALA both require blue light excitation, fluorescein requires a yellow-green emission filter, whereas 5-ALA requires a red emission filter.

Quantum Yield and Brightness

The fluorescence quantum yield (Φ) is defined as the ratio of the number of photons emitted to the number of photons absorbed. For example, PPIX has a Φ of 0.08,[21,22] indicating that for every 100 photons absorbed, 8 will be emitted as fluorescence. For the remainder 92 photons absorbed, the energy will be

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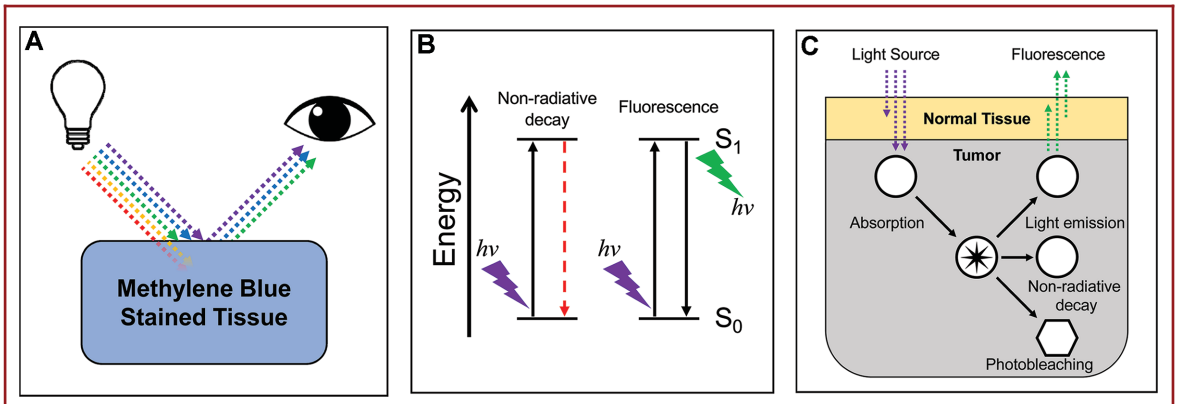


FIGURE 2. **A**, *An illustration depicting the white light illumination of a methylene blue stained tissue.* **B**, *A simplified Jablonski diagram where the vertical axis represents energy, and the horizontal lines represent electronic energy states. Solid arrows represent electronic transitions and dotted red arrows represent non-radiative thermal decay (ie, heat). The violet lightning bolt refers to excitation light from a light source such as the sun. The green lightning bolt represents longer wavelength emission light that occurs in fluorescence.* **C**, *A diagram depicting the numerous processes that occur to obtain a fluorescence signal from a tumor stained with the fluorescent tracer. Light penetrates overlying tissue to excite the fluorescent tracer from its ground state (empty circle) to its excited state (circle with a star), which can degrade to an inactive (hexagon), return to its ground state by releasing energy as heat, or emit light as fluorescence.*

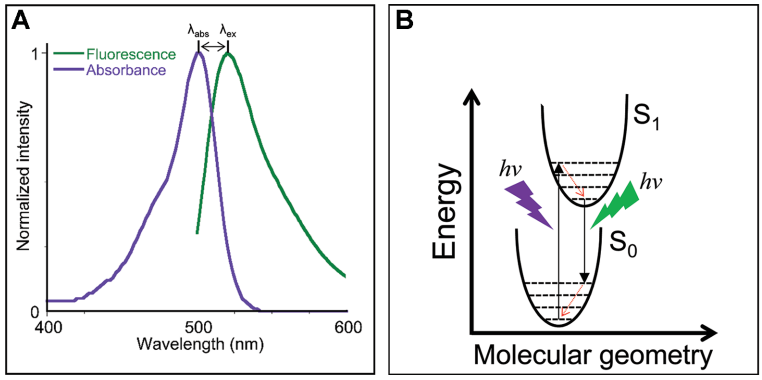


FIGURE 3. **A**, *The absorbance and fluorescence spectra of fluorescein with the wavelengths of maximal light absorption (λ_{abs}) and emission (λ_{em}), and the Stokes shift (double headed arrow) labeled.* **B**, *An elaborated Jablonski diagram in which the x-axis corresponds to the molecular geometry, and each electronic energy state (solid curve) contains numerous vibrational energy states (dotted lines) that correspond to various possible arrangements and motion of the atomic nuclei within the molecule. Solid arrows represent electronic transitions and dotted red arrows represent nonradiative thermal decay.*

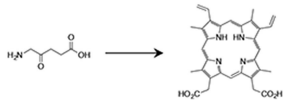
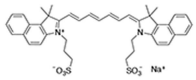
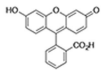
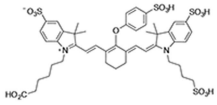
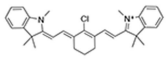
dissipated through nonfluorescent pathways, including heat. Another factor is the molar extinction coefficient (ε), which describes how readily a molecule absorbs light of a given wavelength. Together, the product of ε and Φ gives the brightness, a quantity that describes a molecule's propensity both to absorb and to emit light.

It is important to examine all of these measures together. Many near infrared (NIR) fluorophores, such as ICG, exhibit poorer quantum yields ($\Phi < 0.2$) than visible light fluorophores, such as fluorescein ($\Phi = 0.85$; Figure 4).[23,24] However, the molar extinction coefficients of these longer wavelength fluorophores are often high (>100 000 $M^{-1}cm^{-1}$), and thus examining only the quantum yield would underestimate the overall fluorescent intensity of these NIR fluorophores.

Quenching

Several extrinsic factors, broadly classified as quenching, can decrease fluorescence. Static quenching occurs when fluorophores form dimers, oligomers, or other aggregates.[25-27] Hence, simply

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Fluorophore	Structure	Photophysical properties	References to Clinical Studies
5-ALA/PPIX*		λ_{ex}: 405 nm[18, 122] λ_{em}: 635 nm Stokes shift: 220 nm ϵ: 5000 $M^{-1}cm^{-1}$ Φ: 0.08 Brightness: 400 $M^{-1}cm^{-1}$	7–9,60–72
Indocyanine green* (ICG)		λ_{ex}: 807 nm[18] λ_{em}: 822 nm Stokes shift: 15 nm ϵ: 121,000 $M^{-1}cm^{-1}$ Φ: 0.093 Brightness: 11,000 $M^{-1}cm^{-1}$	95–99
Fluorescein*		λ_{ex}: 489 nm[120,121] λ_{em}: 515 nm Stokes shift: 26 nm ϵ: 88,000 $M^{-1}cm^{-1}$ Φ: 0.85 Brightness: 75,000 $M^{-1}cm^{-1}$	105–110
IRDye 800 CW		λ_{ex}: 786 nm[18] λ_{em}: 800 nm Stokes shift: 14 nm ϵ: 237,000 $M^{-1}cm^{-1}$ Φ: 0.142 Brightness: 34,000 $M^{-1}cm^{-1}$	
BODIPY		λ_{ex}: 505 nm[23] λ_{em}: 511 nm Stokes shift: 6 nm ϵ: 91,000 $M^{-1}cm^{-1}$ Φ: 0.94 Brightness: 86,000 $M^{-1}cm^{-1}$	
IR-775		λ_{ex}: 760 nm[110] λ_{em}: 778 nm Stokes shift: 18 nm	

*: FDA approved

FIGURE 4. *Names, chemical structures, photophysical properties[18,23,125-128], and references to clinical studies of FDA approved fluorophores, fluorophores currently undergoing clinical trials, and fluorophores in preclinical investigation.*

increasing the concentration of a particular fluorophore may not necessarily yield better signal-to-noise ratios. Homotransfer or self-quenching is a type of Förster resonance energy transfer (FRET) that occurs when the fluorophore is at high concentrations in solution (>100 μM) or locally (eg, many bound to 1 protein molecule), and the energy of S_1 is transferred to another fluorophore rather than emitted as fluorescence.[28,29] A related phenomenon is the inner filter effect, which starts at lower concentrations (1-10 μM), where emitted light is absorbed by fluorophores directly in its path.

Some fluorogenic tracers leverage FRET to produce a signal in response to a trigger. Fluorophores can be coupled to quenchers via a linker that breaks when exposed to low pH[30,31] or tumor-specific enzymes.[32,33] Once the fluorophore and quencher are separated, the quenching effect is eliminated and fluorescence is restored. For example, an ICG-labeled polymer disaggregates at pH 6.9, eliminating self-quenching and producing a >100-fold "turn-on" of fluorescence.[30]

Quenching can interfere with FGS. ICG fluorescence in blood increases as concentration increases until 50 to 80 μg/mL, whereupon further increases in concentration result in less fluorescence.[34-36] The underlying mechanism includes a combination of static quenching,[37-39] self-quenching,[40] and the inner filter effect.[40] Clinically, quenching may impact the imaging of tumors that are particularly tracer-avid. Thus, although counterintuitive, there may be select instances where lower concentrations of ICG, or other similarly behaved tracers, would yield superior results.

Photobleaching

Photobleaching is the degradation of fluorophores upon irradiation with light. Excited fluorophores may react with oxygen or other molecules to irreversibly generate nonfluorescent products.[41,42] The rate of photobleaching depends on the chemical reactivity of the fluorophore and the intensity of the excitation light. Photostability is related to the fluorescent quantum yield because nonradiative pathways, such as intersystem crossing, are often involved. The fluorescence quantum yield of PPIX is 0.08, whereas the intersystem crossing quantum yield—the frequency by which PPIX in its excited state undergoes this particular form of nonradiative decay—is 0.76.[21] Thus, PPIX

is nearly 10 times more likely to undergo intersystem crossing to enter a triplet state that is highly reactive with oxygen than to emit light as fluorescence. Although this property is undesirable in FGS, it is leveraged in photodynamic therapy to generate reactive oxygen species locally to damage tumor cells.

Sufficient photostability is critical because there may be a need for extended periods of fluorescence illumination to guide critical portions of a procedure. In a study of ex vivo human brain tumors resected under 5-ALA guidance, the fluorescence signal decayed to 36% of the initial intensity after 16 min of continuous violet-blue light illumination and 29 min of continuous white light illumination.[43] Although in practice, photobleaching may be delayed by the presence of surgical instruments, cotton pads, and overlying tissue, photobleaching may become problematic if tumor is exposed to light too long.

Autofluorescence and Tissue Penetration of Light

Autofluorescence arises from the natural fluorescence of human tissue, often due to endogenous fluorophores, such as amino acids (eg, tryptophan), enzymatic cofactors (eg, flavin adenine dinucleotide), and hemoglobin. Autofluorescence is greatest at shorter wavelengths (300-550 nm),[44-47] and studies of PPIX in in vivo human brain tissue confirmed that autofluorescence is at a minimum at wavelengths greater than 600 nm.[43] When using video-assisted fluorescence detection, emitted light overamplification can produce to undesired fluorescence signal of normal tissues, even when using fluorophores in the red and NIR range.[48]

A related effect is the absorption of light by tissues. A window exists between 600 and 1000 nm where light absorption by biomolecules (<600 nm) and water (>1000 nm) is at a minimum.[28,49] Studies in cadaveric human brains and animal models have demonstrated that red-NIR range light can penetrate between 2 and 8 mm of brain tissue as defined by 1% transmittance at that depth.[50-54] In contrast, light at shorter wavelengths has >5-fold poorer penetrance, largely due to increased light absorption. Nonspecific light scattering also reduces the amount of light that penetrates the brain; however, this effect is only slightly diminished at longer wavelengths.[55] With red and NIR fluorophores, fluorescence can be observed to penetrate through overlying cortical or dural tissue, which may be useful for guiding the initial durotomy or corticotomy.[48,56]

Although both red and NIR fluorophores are advantageous in terms of the increased tissue penetrance of their emitted light, there are nonetheless several important differences between them. NIR fluorescence is not visible to the naked eye and must be visualized using a specialized camera. In contrast, red fluorescence can be directly observed by the naked eye, but there can be more interference from ambient light.[48] In all cases, the fluorophore and the visualization system should be appropriately matched to best highlight the tumor against a clear background of normal tissue.

FDA APPROVED FLUOROPHORES

In this section, we discuss additional optical and physical properties of these agents, highlighting advantages afforded by their unique molecular properties as well as examining shortcomings that may limit their use. In terms of their clinical performance, we kindly refer the reader to a number of excellent articles and reviews available in the recent literature (Figure 4).[14,15,18,57-59]

5-Aminolevulinic Acid

5-ALA[7-9,60-72] is an endogenous building block in the heme synthesis pathway. It was first approved as Gliolan® (medac GmbH, Wedel, Germany) in the EU in 2007, and was recently approved by the FDA in the USA in 2017. It is orally administered to patients at a dose of 20 mg/kg 3 h before surgery, and is naturally converted to PPIX, a fluorescent precursor to heme that accumulates in glioma tissues due to increased local blood-brain barrier (BBB) permeability and PPIX synthesis.[73-77] Upon violet-blue light illumination, PPIX emits red fluorescence in the bulk of the tumor and pink fluorescence at margins. The fluorescence in the visible light range may be advantageous because direct visualization with the naked eye may offer improved discrimination between fluorescing and nonfluorescing tissue.[48] Inadequately calibrated imaging systems may underamplify, overamplify, or distort the fluorescence produced by the tumor, as well as the trace fluorescence and autofluorescence signal from the surrounding tissues. Maximum fluorescence is observed 6 to 8 h after administration, and the side effect profile is minimal at this dosage. Furthermore, 5-ALA has also been combined with other imaging modalities, including an intraoperative MRI, neuronavigation, and sonography, and has been investigated in other tumor types, including meningiomas and metastases.[62,78-81]

One of its limitations is low fluorescence signal in some low-grade tumors and at tumor margins due to reduced accumulation of fluorophore, which is often less than 0.1 μg/mL.[11,61,82-88] Moreover, PPIX is less bright than other fluorophores, such as ICG, which is 27 times brighter, and fluorescein, which is 180 times brighter (Figure 4). PPIX concentrations of 1 to 10 μg/mL emit clearly visible fluorescence, and, quantitative fluorescence techniques in combination with signal processing algorithms have increased detection of PPIX fluorescence down to concentrations of 0.01 μg/mL.[89-94] Nonetheless, with increased detection sensitivity, nonspecific accumulation of PPIX within normal brain tissue and dura, which ranges from 0.001 to 0.1 μg/mL,[83,92] may impact the delineation of tumor boundaries. This highlights the limitation of existing tracers and the need for improved molecular targeting so that smaller amounts of tumor tissue and lower grade tumors can be clearly identified.

Indocyanine Green

ICG,[95-98,56] the first and only FDA approved NIR fluorophore, is indicated for determining cardiac output, liver

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function, and liver blood flow, ophthalmic angiography, and assessing tissue perfusion. It is a hydrophobic cyanine dye that binds tightly to plasma proteins, confining it to the intravascular space, and thus it can be used for angiography, cerebrovascular surgery, imaging lymph node drainage, and defining intracerebral vasculature during brain tumor resection.[99-102] Furthermore, it has a very low rate of adverse reactions (<0.1%).[103]

Recently, a novel technique called "Second Window ICG" has been described, in which high-dose ICG (5.0 mg/kg) is administered 24 h prior to surgery, rather than the a lower dose (2.5 mg/kg) given intraoperatively (Figure 5, see **Video**, **Supplemental Digital Content**).[103] During the 24-h period, ICG accumulates within tumor tissue due to a combination of a local BBB disruption, relative lack of lymphatic drainage, and hypoxic tumor microenvironment.[56] In a rodent model of glioblastoma multiforme (GBM), the fluorescence signal peaked at 1 h after administration, decreased rapidly over the next 6 h, and reached a plateau that persisted for at least 48 h. Trials in humans demonstrated signal-to-background ratios at 24 h that were consistent with predictions from the animal studies.[97] The stability of the fluorescence signal within this sustained "second window" may yield comparable signal characteristics even between patients with GBM, potentially allowing for more consistent fluorescence visualization of tumors.

Fluorescein

Fluorescein[104-109] is a well-tolerated yellow-green xanthine fluorophore that is indicated for ophthalmic angiography and corneal staining, and can be used in cerebrovascular procedures and to detect cerebrospinal fluid leaks.[110,111] Fluorescein is a passive agent and extravagates from the vasculature into tissues where the BBB is disrupted, which are not definitively nor exclusively restricted to tumor tissue and may be found in areas of edema or surgical injury.[112,113] Furthermore, fluorescein accumulation within the tumor is dependent on BBB breakdown and vascular permeability, which may not be consistently observed in all tumor types. Nonetheless, fluorescein is distinguished by its high brightness, which yields a robust signal even at lower concentrations. In a GBM case, strong tumor fluorescence was observed within seconds after intravenous administration.[114] A recent report demonstrated the use of fluorescein with 5-ALA in multicolor FGS, where the nonspecific accumulation of fluorescein within brain tissue was uniquely leveraged to provide a yellow-green background to contrast against the pink-red fluorescence of PPIX within the tumor tissue.[115] Two excitation sources were used; however, a single long-pass filter allowed the simultaneous visualization of fluorescein and PPIX fluorescence.

Fluorescent Tracers in Preclinical Development and Clinical Trials

Although ICG and fluorescein are convenient because of their regulatory status, they are not considered tumor-specific dyes due to their lack of a defined molecular target, and thus can have poor tumor margin definition. Many novel tracers currently in development improve tumor-specificity using favorable red or NIR fluorophores appended to targeting groups. The optical properties of these fluorophores are similar to those of the fluorophores described above, and will be the focus of the discussion in this section. Overall, increased selectivity of the accumulation of these tracers in tumor tissue would improve the signal-to-background ratio, allowing for sharper contrast between pathologic and healthy tissue.

ABY-029 and Cetuximab-IRDye-800

ABY-029 is a synthetic bioconjugate of a 58-amino-acid anti-EGFR Affibody® (Z03115) (Affibody AB, Solna, Sweden) and IRDye®-800 CW (Li-Cor, Lincoln, Nebraska). EGFR is overexpressed in approximately 50% of GBM, and has been pursued as a therapeutic and diagnostic target in a number of different cancers.[116] An anti-EGFR antibody, cetuximab® (Eli Lilly and Company, Indianapolis, Indiana), has also been conjugated to IRDye®-800 CW, and has demonstrated utility in studies of human and mouse head and neck squamous cell carcinomas.[117] IRDye®-800 CW, a cyanine fluorophore like ICG, is a popular choice because it emits in the NIR, can be easily conjugated to targeting moieties, and has a good brightness (Figure 4). Recently, there is a growing trend favoring IRDye®-800 CW because of its approximately 3-fold greater brightness over ICG, versatility, and safety profile. Furthermore, with the advancement in imaging technologies, the advantages of increased light penetration through tissues and decreased autofluorescence in the NIR are outweighing some of the early challenges of light detection and image processing.

Alkylphosphocholine analogs—CLR1501 and CLR1502

These alkylphosphocholine analogs contain a phospholipid-like molecule conjugated with a green BODIPY fluorophore (CLR1501) or a NIR IR-775 fluorophore (CLR 1502) (Cellectar Biosciences, Madison, Wisconsin). Tumor cells accumulate more phospholipids within their cell membranes due to their increased abundance of lipid rafts and decreased phospholipid metabolism.[118,119] BODIPY is similar to fluorescein in its yellow-green fluorescence and its very high brightness. Conjugation of BODIPY to a targeting unit leverages the strong fluorescence of the fluorophore while improving the specificity of fluorophore accumulation within the tumor. IR-775 is a cyanine dye like ICG, and although its emission is blueshifted relative to that of ICG, it remains well within the NIR range.

BLZ-100

BLZ-100 (Blaze Bioscience Inc, Seattle, Washington) consists of the 36-amino-acid chlorotoxin peptide and ICG. Chlorotoxin is found in the venom of the Deathstalker scorpion (*Leiurus quinquestriatus*) and binds to chloride channels, annexin A2, and matrix metalloproteinase 2.[120] A study found that >90% of human brain tumor samples, including gliomas, demonstrate abundant binding of chlorotoxin, whereas normal tissue was consistently negative.[121] Thus, chlorotoxin has been used widely as a targeting moiety for a variety of payloads.[120]

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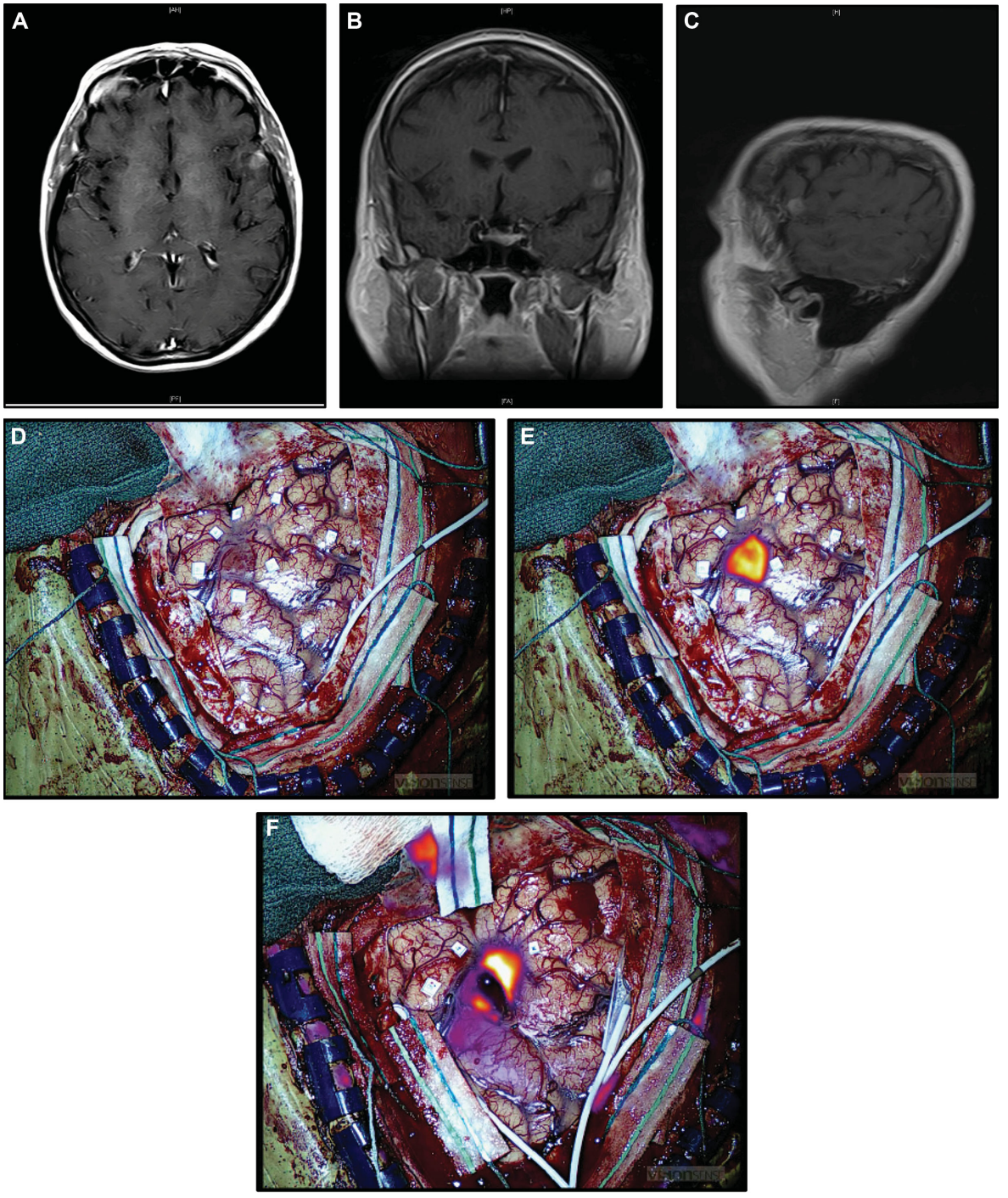


FIGURE 5. *Second window ICG.* **A**-**C**, *MRI images of a left temporal glioblastoma.* **D**, *Nomal white light illumination. NIR fluorescence color-mapped in real time with an overlay of the visible light color view using a VisionSense Iridium camera system* **E**, *after dural opening and* **F**, *during tumor resection.*

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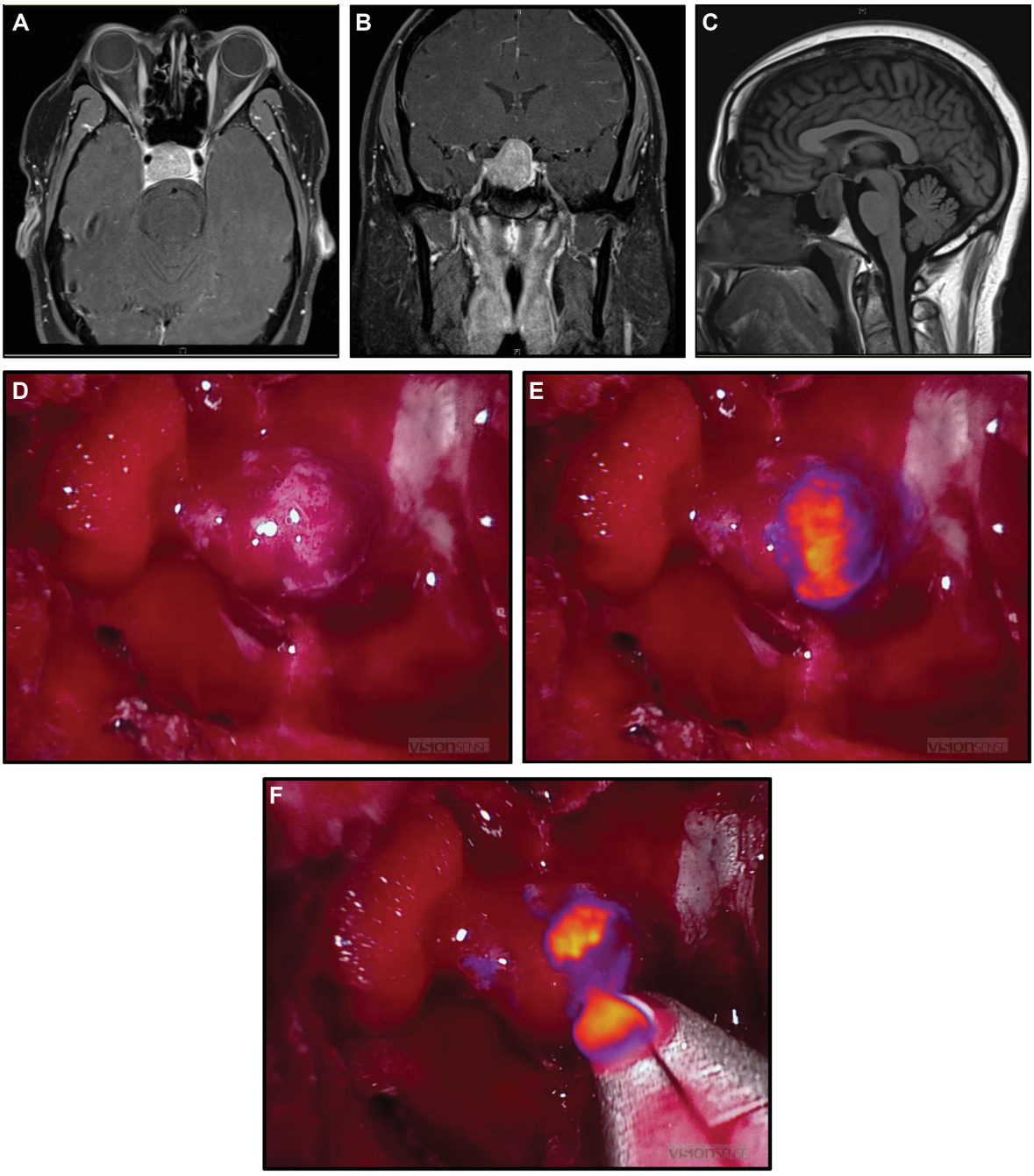


FIGURE 6. *OTL-38.* **A–C**, *MRI images of a FRα overexpressing, nonsecretory, null-cell pituitary adenoma.* **D**, *Nomal endoscopic white light illumination. NIR fluorescence color-mapped in real time with an overlay of the visible light color view using a VisionSense Iridium camera system* **E**, *before and* **F**, *during tumor resection.*

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EC17 and OTL38

EC17 (On Target Laboratories, West Lafayette, Indiana) and OTL38 (On Target Laboratories, West Lafayette, Indiana) are bioconjugates of a folate analog and fluorescein or a cyanine fluorophore, respectively, that target folate receptor alpha (FRα).[122] FRα is overexpressed in many different cancers, especially in nonfunctional pituitary adenomas, but not in functional pituitary adenomas (Figure 6).[123] The custom cyanine dye is similar to ICG, and has an λ_{abs} of 775 nm and λ_{em} of 794 nm. Given the improved tissue penetration and decreased autofluorescence in the NIR, OTL38 demonstrates a treater signal-to-background ratio, and has been favored over EC17.[124]

CONCLUSION

Since the first observation more than 50 yr ago that fluorophores could be used to 'light up' brain tumors, there has been tremendous advancement in the field of FGS. Ongoing challenges include precision imaging of low-grade tumors and tumor margins, which remain difficult due to insufficient or inconsistent tumor signal against background tissue. Addressing this problem includes improving the tumor selectivity of the tracer, its fluorescent properties in vivo, and the accompanying visualization technology, and as such, the field has moved towards leveraging molecular targeting, adopting NIR fluorophores, and using video-assisted imaging systems. Future applications may also include combination with other imaging modalities and intraoperative diagnostic technologies. As demonstrated by the progress thus far, continued multidisciplinary collaboration will be needed to develop novel technologies that will prove their worth in clinical trials and, ultimately, help the surgeon perform the best possible surgery.

Disclosures

This work was supported in part by the National Institutes of Health (grant no. R01 CA193556 awarded to SS) and the Institute for Translational Medicine and Therapeutics of the Perelman School of Medicine at the University of Pennsylvania (awarded to JYKL). Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR001878 (awarded to JYKL). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr Lee owns stock options in Visionsense. Dr Singhal holds patent rights over some technologies presented in this review.

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Supplemental Digital Content. Video. Second Window ICG. A video demonstrating real-time overlay of NIR fluorescence with white light illumination during tumor resection.

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COMMENTS

Fluorescenece guided surgery is a rapidly changing field and the authors present a comprehensive review covering the basic science of this intraoperative technology. They offer a discussion of the various agents and their advantages and disadvantages. They also cover the agents that are undergoing or will be soon to enter clinical trials. These agents are becoming an important topic and potentially useful tool in brain tumor surgery both to determine extent of resection and to confirm presence of tumor tissue on needle biopsy.[1,2]

The section of FDA approved fluorophores is comprehensive. They discuss intraoperative MRI and the use of fluorescence in multiple tumor types. Beyond this, however, the practical knowledge discussion is limited and beyond the scope of this article. In summary, this review provides a thorough discussion of the various compounds and the science behind them making this a primer useful to most neurosurgeons.

Jeffrey Leonard
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1. Jenkinson MD, Barone DG, Bryant A, Vale L, Bulbeck H, Lawrie TA, Hart MG, Watts C. Intraoperative imaging technology to maximize extent of resection for glioma. *Cochrane Database Syst Rev.* 2018;1:CD012788.
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The authors have written a review article of fluorescent agents used as an adjunct for neurosurgical procedures. They have focused their review primarily on procedures for resection of neoplasms. The paper nicely summarizes the physics and chemistry of the fluorescent agents that are approved for use and also addresses a number of agents in development. The authors direct the reader to references of clinical studies so that they can focus their review primarily of the chemical properties of fluorescence.

Additional fluorescent issues not discussed by the authors include practical considerations in the use of these agents, such as dose and timing of administration, types of microscope filters needed, cost of equipment and materials needed for clinical incorporation into practice, availability and ease of acquisition of the agents, side effects, potential toxicities, and interpretive difficulties in the use of these agents. Some of these topics have been partially addressed by others.[1,2] So, as a primer, this paper helps the neurosurgeon understand the chemistry of fluorescence better. But practical considerations will need to come from elsewhere.

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1. Liu JT, Meza D, Sanai N. Trends in fluorescence image-guided surgery for gliomas. Neurosurgery. 2014;75(1):61-71.
2. Li Y, Rey-Dios R, Roberts DW, Valdés PA, Cohen-Gadol AA. Intraoperative fluorescence-guided resection of high-grade gliomas: a comparison of the present techniques and evolution of future strategies. World Neurosurg. 2014;82(1-2):175-85.

The successful approval and use of 5-ALA for intraoperative guidance in GBM resection has placed fluorescence guided surgery (FGS) at the leading edge of tumor neurosurgery. The authors present a timely review of FGS with an emphasis on the fundamentals of fluorescence. As they presented clearly, the modality of fluorescence is governed by unique photophysics including photobleaching and quenching. A nuanced understanding of this intraoperative imaging modality, including its limitations, will allow neurosurgeons to further advance and apply FGS in the operating room. As the field and technology of FGS develops through the requisite multidisciplinary input from neurosurgeons, chemists, and engineers, better ways to characterize and apply this modality in the operating room will improve the safety and effectiveness of tumor resections and possibly patient outcomes.

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Papillary Tumor of the Pineal Region: Systematic Review and Analysis of Prognostic Factors

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The abstract of this manuscript was presented at the "XXXII Congresso Brasileiro de Neurocirurgia" at Porto Alegre, Brazil on September 7, 2018.

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Received, May 17, 2018.
Accepted, February 8, 2019.
Published Online, April 15, 2019.

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BACKGROUND: Clinical outcomes and biological behavior of papillary tumors of the pineal region (PTPR) are still under investigation. The best therapeutic strategy has not been defined.

OBJECTIVE: To perform a comprehensive patient-level analysis of all PTPR cases and identify their clinical features, treatment options, and prognostic factors.

METHODS: A search of the medical databases for case series and reports on PTPRs from January 2003 to June 2017 was performed. Data addressing PTPR's clinical presentation, imaging, treatment, and histological features were. Variables associated with the primary outcome of 36-mo survival were identified through Cox regression models.

RESULTS: The initial search yielded 1164 studies, of which 71 were included (60 case reports and 11 case series), containing 177 patients (mean age 33.0 ± 15.3 yr and 53.2% male). Intracranial hypertension and hydrocephalus prevailed as the clinical picture. Surgery was performed on 82.0% and gross total resection (GTR) was achieved on 71.4%. A total of 56.8% recurred after a median 29 mo (quartiles 10.5-45.5). The 36-mo survival rate was 83.5% (95% confidence interval [CI] 76.2-89.2%). Good functional outcomes (Glasgow Outcome Scale 4/5) were observed in 60.0%. The variables of interest were inconsistently reported and the multivariable analysis final sample was 133 patients. After adjustment for age, tumor size (each additional centimeter, hazard ratio [HR] 1.99, 95% CI 1.12-3.53, $P = .019$) and surgical treatment (HR 0.16, 95% CI 0.05-0.45, $P = .001$) were associated with 36-mo survival.

CONCLUSION: Tumor size and surgery are associated with improvement in 36-mo survival. We did not observe any significant benefits from GTR or adjuvant treatments.

KEY WORDS: Brain neoplasms, Pineal gland, Papillary tumor of the pineal region, Systematic review, Meta-analysis

Neurosurgery 85:E420–E429, 2019 DOI:10.1093/neuros/nyz062 www.neurosurgery-online.com

Tumors in the pineal region are rare, representing less than 1% of all intracranial tumors in adults.[1-3] Nearly 17 histological tumor types have been described for pineal tumors, each with different oncologic behaviors.[2] The papillary tumor of the pineal region (PTPR) is the most recently identified type of pineal tumor. It was described in 2003 by Jouvet et al[4] and included in the 2007 World Health Organization (WHO) classification of central nervous system tumors.[5,6] Its origin is from the ependymal cells of the subcommissural organ with epithelial-like growth patterns and fibrovascular papillae associated with a well-defined secretory function.[4,7,8] Immunoreactions against cytokeratin, vimentin, and S100 proteins, and variable reactivity with glial fibrillary acid protein (GFAP) and epithelial membrane antigen (EMA)[4] represent typical characteristics of the PTPR through immunohistochemical evaluation.

Noncommunicating acute hydrocephalous due to the obliteration of the cerebral aqueduct is a common clinical presentation of PTPR.[9,10] Radiologically, this is depicted as a heterogeneously enhancing mass with cystic

ABBREVIATIONS: CI, confidence interval; **EMA,** epithelial membrane antigen; **GOS,** Glasgow Outcome Scale; **GFAP,** glial fibrillary acid protein; **GTR,** gross total resection; **HR,** hazard ratio; **MRI,** magnetic resonance imaging; **NSE,** neuron-specific enolase; **PTPR,** papillary tumors of the pineal region; **QTx,** chemotherapy; **RTx,** radiotherapy; **SRS,** stereotactic radiosurgery; **WHO,** World Health Organization

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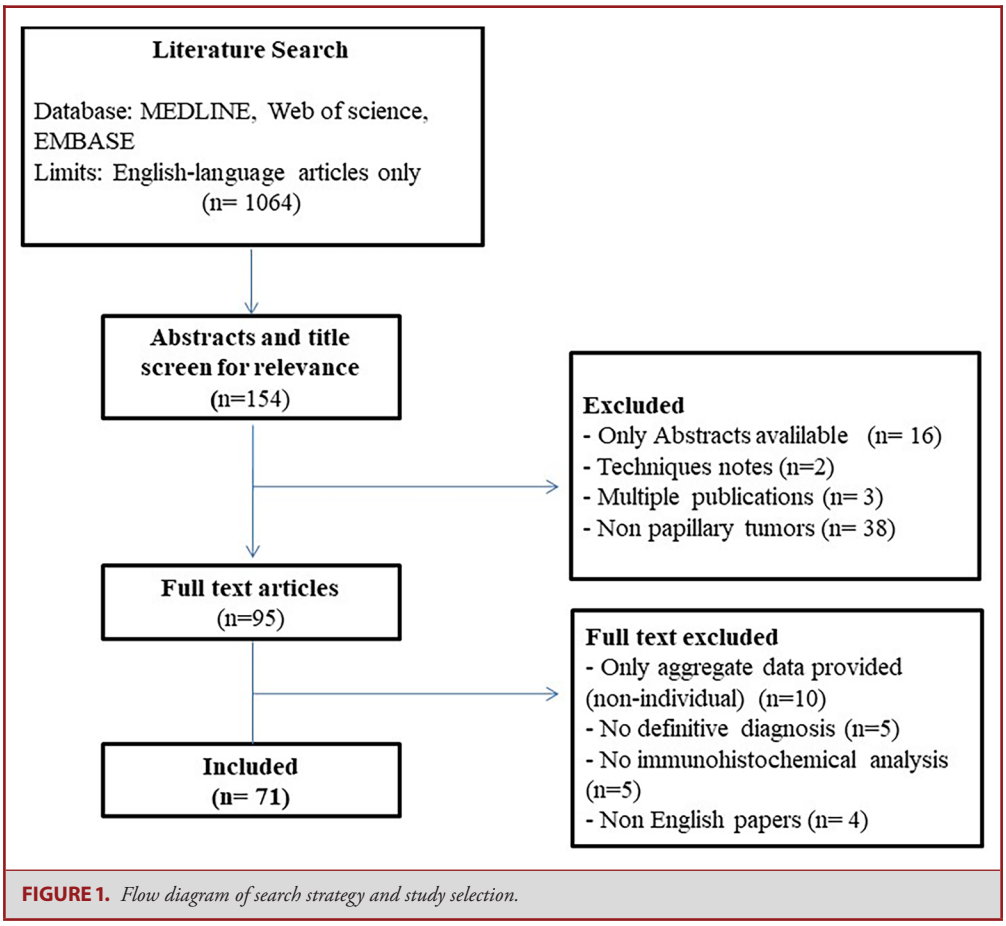


FIGURE 1. *Flow diagram of search strategy and study selection.*

components.[11-13] Due to the recent identification of PTPRs, no valid histologic grading system or standard treatment options exist for this type of tumor. In previous series, only gross total resection (GTR) resulted in longer overall survival.[9,14] In addition, the role of adjuvant treatments has not yet been determined.[9,10]

To study the factors associated with better survival, we performed a comprehensive patient-level analysis of all PTPR cases reported in the last 15 yr.

METHODS

Literature Search

We performed a search in the Web of Sciences, Medline, and EMBASE databases for case series or case reports on PTPRs published between January 2003 and June 2017, using the following keywords in both AND and OR combinations: "papillary," "tumor," "pineal," "gland," "treatment," "surgery," "outcome," and "follow-up." The keywords were searched in "all fields" modality. Studies were independently evaluated for inclusion criteria by 2 authors (Vitor Nagai Yamaki and Davi Jorge Fontoura Solla). In cases of disagreement, a third author (Eberval Gadelha Figueiredo) made the final decision.

Study Selection

Case series or case reports with histologically-proven PTPR cases that met the 2007 WHO classification criteria were included in our review. Individuals of any age were included. Studies without individual patient-level data were excluded. Papers were carefully scanned for duplications. If duplications occurred, the most recent description was selected (Figure 1). Papers were stratified into 5-yr intervals for descriptive purposes.

Data Abstraction

We collected data regarding the clinical presentation, imaging, treatment, and histologic features of PTPRs, including (1) clinical pictures, (2) magnetic resonance imaging (MRI) characteristics and tumor extensions, (3) procedures prior to treatment (such as ventriculoperitoneal shunts, ventriculostomies, and biopsies), (4) treatment modalities (such as surgery, radiosurgery, radiotherapy [RTx], and chemotherapy [QTx]), (5) the Glasgow Outcome Scale (GOS) at final follow-ups, (6) survival, (7) histologic features (such as mitosis rates and presence or absence of necrosis), and (8) immunohistochemical markers (such as cytokeratin, vimentin, S100 proteins, synaptophysin, GFAP, and EMA). The median follow-up was 36 mo and, therefore, we defined a 36-mo survival as the primary outcome. The GOS was selected as the standard functional outcome score.

If original papers did not report the GOS, reported functional scales were used to obtain these data according to the respective degree of dependency.

Statistical Analysis

For descriptive purposes, categorical variables were presented through relative and absolute frequencies. Normally distributed continuous data were presented as mean and standard deviations and, otherwise, by median and quartiles.

Potential predictors of 36-mo survival were identified through the Kaplan-Meier method, using the Log-rank (Mantel-Cox) test to compare the survival functions. Continuous variables were analyzed through a univariate Cox regression. The variables considered for inclusion on the multivariable Cox regression model were patient's age (predetermined, due to biological plausibility) and those variables significant at the univariate analysis at $P < .10$. Hydrocephalus and preoperative biopsies fulfilled the criteria based on the univariate results, but their incidences were too low to permit inclusion on the multivariable model without creating relevant instability. Results were presented through hazard ratios (HR) and 95% confidence intervals (CI). The proportionality and linearity assumptions were verified using graphical methods and the Schoenfeld and Martingale residuals, respectively.

All tests were 2-sided and final P values under .05 were considered to be statistically significant. All analyses were conducted with the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 24.0.; IBM, Armonk, New York) software.

RESULTS

A systematic search yielded 1164 studies, 71 of which were included (60 case reports and 11 case series). These studies contained 177 total patients. The study selection process is summarized in Figure 1. Although 15 yr have passed since the first description of PTPRs, meaningful changes in histopathological features and treatment have not been observed (Table 1).[15-76] The variables of interest were inconsistently reported and these are the amount of missing information: clinical picture 77 (43.5%), hydrocephalus 62 (35.0%), symptoms duration 125 (70.6%), tumor size 31 (17.5%), surgical treatment 10 (5.6%), RTx 4 (2.3%), QTx 4 (2.3%), recurrence 57 (32.2%), functional outcome 99 (55.9%), and survival 38 (21.5%). Age and gender had no missing information.

Our analysis found PTPR predominantly in young adults (33.0 ± 15.3 yr), with a slightly higher proportion of male patients (53.2%). Headache with intracranial hypertension was the most common warning sign (82.9%), followed by visual disturbance (45.7%). Computed tomography scan diagnosed hydrocephalus in 88.6% of the cases and half underwent urgent shunt derivation or ventriculostomy. On MRI, PTPR was characterized by a partially cystic pineal region mass with heterogeneous enhancement, measuring approximately 3 cm (2.9 ± 1.0 cm). Extension to the third ventricle associated with cerebral aqueduct obstruction was present in 67.6% of cases. Extension to the lateral ventricles was present in 13.3% and to the fourth ventricle in 3.0%.

TABLE 1. Included Studies Stratified in 15 yrs Interval

Year	No. of studies	Type of study	No. of patients	Gender (female)	Age (mean, yr)	Tumor Size (mean, cm)	Clinical onset		Treatment modalities		Disease free-interval (mean, mo)	Follow-up (mean, mo)
2003-2007	7	Case reports	5[1,15-18]	25/45 (55.5%)	34.0 ± 14.5	2.8 ± 1.0	Headache	6/7 (85.7%)	Surgery	38/45 (84.4%)	33.7 ± 22.2	61.0 ± 49.3
									SRS	4/45 (8.8%)		
		Case series	2[17,19]				Visual disturb	2/7 (28.5%)	RTx	26/45 (57.5%)		
							Ataxia	1/7 (14.2%)	QTx	6/45 (13.3%)		
2008-2012	38	Case reports	35[8,12,13,20-49]	25/58 (43.1%)	34.0 ± 14.7	2.8 ± 1.0	Headache	44/54 (81.4%)	Surgery	43/56 (76.7%)	34.0 ± 33.2	57.0 ± 69.5
									SRS	3/56 (5.3%)		
		Case series	3[50-52]				Visual disturb	27/54 (50%)	RTx	29/56 (51.7%)		
							Ataxia	13/54 (24%)	QTx	6/56 (10.7%)		
2013-2017	26	Case reports	23[53-75]	37/74 (50.0%)	33.1 ± 16.5	2.9 ± 1.0	Headache	28/39 (71.7%)	Surgery	57/66 (86.3%)	33.0 ± 29.7	54.8 ± 47.7
									SRS	9/66 (13.6%)		
		Case series	3[9,10,76]				Visual disturb	5/39 (12.8%)	RTx	25/66 (37.8%)		
							Ataxia	12/39 (30.7%)	QTx	6/66 (9.0%%)		
Total	71		177									

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TABLE 2. Clinical and Imaging Characteristics and Procedures Before Definitive Treatment According to 36-mo Survival

Variables	General (139)	36-mo survival		*P* value[a]
		Dead (16)	Alive (123)	
Gender				.385
Female	65/139 (46.8%)	9/16 (56.3%)	56/123 (45.5%)	
Male	74/139 (53.2%)	7/16 (43.8%)	67/123 (54.5%)	
Age (mean ± SD, yr)	33.4 ± 15.4	35.9 ± 13.7	33.4 ± 15.9	.510
Clinical onset				
Headache	58/70 (82.9%)	2/2 (100%)	56/68 (82.3%)	.542
Ataxia	15/70 (21.4%)	1/2 (50.0%)	14/68 (20.5%)	.441
Visual disturbances	32/70 (45.7%)	2/2 (100%)	30/68 (44.1%)	.183
Parinaud's syndrome	8/70 (11.4%)	0/2 (0.0%)	8/68 (11.7%)	.629
Symptoms duration (median and quartiles, mo)	2.0 (1.0-6.0)	2.5 (1.0-4.0)	2.0 (1.0-8.0)	.749
Imaging characteristics				
Cystic component	52/65 (80.0%)	2/2 (100%)	50/63 (79.3%)	.549
Gadolinium enhancement	63/65 (96.9%)	2/2 (100%)	61/63 (96.8%)	.778
Lateral ventricle extension	8/60 (13.3%)	0/2 (0.0%)	8/58 (13.8%)	.566
III Ventricle extension	44/65 (67.6%)	2/2 (100%)	42/63 (66.6%)	.387
IV Ventricle extension	2/65 (3.0%)	0/2 (0.0%)	2/63 (3.1%)	.769
Hydrocephalous	70/79 (88.6%)	2/4 (50.0%)	68/75 (90.6%)	.012
Tumor size (mean ± SD, cm)	2.8 ± 1.0	3.4 ± 1.0	2.7 ± 1.0	.018
Tumor volume (mean ± SD, cm^3)	8.3 ± 7.1	14.0 ± 11.2	7.8 ± 7.2	.580
Procedures before treatment				
Ventriculoperitoneal shunt	29/69 (42.0%)	1/4 (25.0%)	28/65 (43.1%)	.385
Ventriculostomy	18/62 (29.0%)	1/4 (25.0%)	17/58 (29.3%)	.956
Biopsy	38/78 (48.7%)	6/6 (100%)	32/72 (44.4%)	.018

Data presented as valid n (%), except if otherwise specified.
SD: Standard deviation.
[a]Survival analysis by the log-rank test (categorical variables) or Cox regression (continuous variables).

Three yr after diagnosis, 83.5% (95% CI 76.2-89.2%) of the patients were alive and good functional outcomes (GOS 4 or 5) were observed in 60.0% at the last follow-up available. On univariate survival analysis, no demographic or clinical characteristic was associated with 36-mo survival. The median time delay for treatment following detection of the first symptoms was 2 mo (quartiles 1-6), without significant implications for the outcome. Larger tumors were associated with decreased 36-mo survival (3.4 ± 1.0 vs 2.7 ± 1.0 cm, $P = .018$; Table 2).

Most patients underwent surgical resection (82.0%), which was associated with increased survival at 36 mo ($P < .001$) in univariate analysis (Table 3 and Figures 2 and 3). However, the extent of resection did not affect outcomes; GTR did not increase survival compared to nontotal resection. Other treatment modalities, such as RTx (44%), QTx (10.3%), and radiosurgery (10.8%) did not improve survival. Patients submitted to GTR were as likely to receive adjuvant therapy as those who underwent nontotal resection (QTx 13.6% vs 15.2%, $P = .778$; RTx 53.4% vs 42.4%, $P = .282$; radiosurgery 3.4% vs 9.1%, $P = .342$; brachytherapy 0.0% vs 3.1%, $P = .267$). Due to the limited sample size and heterogeneous definitions used, patients submitted to "partial," "subtotal," or "incomplete" resection were analyzed as part of the nontotal resection group. Individual analysis for each treatment modality, such as adjuvant or isolated RTx, stereotactic radiosurgery (SRS), and adjuvant or isolated QTx, was not reliable due to inherent features of the sample.

The median follow-up was 36 mo (quartiles 15-84). Although the tumor's biological behavior has not been well defined, local recurrence has marked PTPR follow-up. Our study demonstrated local recurrence in 57.6%. Survival was not influenced by recurrence. Tumor size was the only independent variable associated with recurrence. Tumors that did not recur had a mean size of 2.5 ± 1.0 cm, while those that recurred had a mean size of 3.1 ± 1.0 cm ($P = .003$; Table 4). We could not evaluate histologic features on risk of recurrence due to the amount of missing information on this regard. We have not included details of the immunohistochemical markers due to the limited amount and heterogeneity of the information.

After multivariable analysis, tumor size (each additional centimeter, HR 1.98, 95% CI 1.11-3.53, $P = .019$) and surgical treatment (HR 0.16, 95% CI 0.05-0.45, $P = .001$) were shown to be associated with 36-mo survival (Table 5 and Figure 3). Older patients demonstrated a tendency to worse prognosis but

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TABLE 3. Treatment of PTPR

Variables	General (139)	36-mo survival		*P* value[a]
		Dead (16)	Alive (123)	
Treatment				
Surgery	114/139 (82.0%)	8/16 (50.0%)	106/123 (86.1%)	<.001
RTx	69/138 (44.0%)	11/16 (68.7%)	58/122 (47.5%)	.456
QTx	18/138 (10.3%)	3/16 (18.7%)	15/122 (12.2%)	.661
Radiosurgery	15/139 (10.8%)	1/16 (6.2%)	14/123 (11.4%)	.211
Extent of resection				.186
GTR	75/105 (71.4%)	4/8 (50.0%)	71/97 (73.2%)	
Non-total resection[b]	30/105 (28.6%)	4/8 (50.0%)	26/97 (26.8%)	

Data presented as valid n(%).
[a]Survival analysis by the log-rank test.
[b]Includes subtotal, partial or incomplete resections.

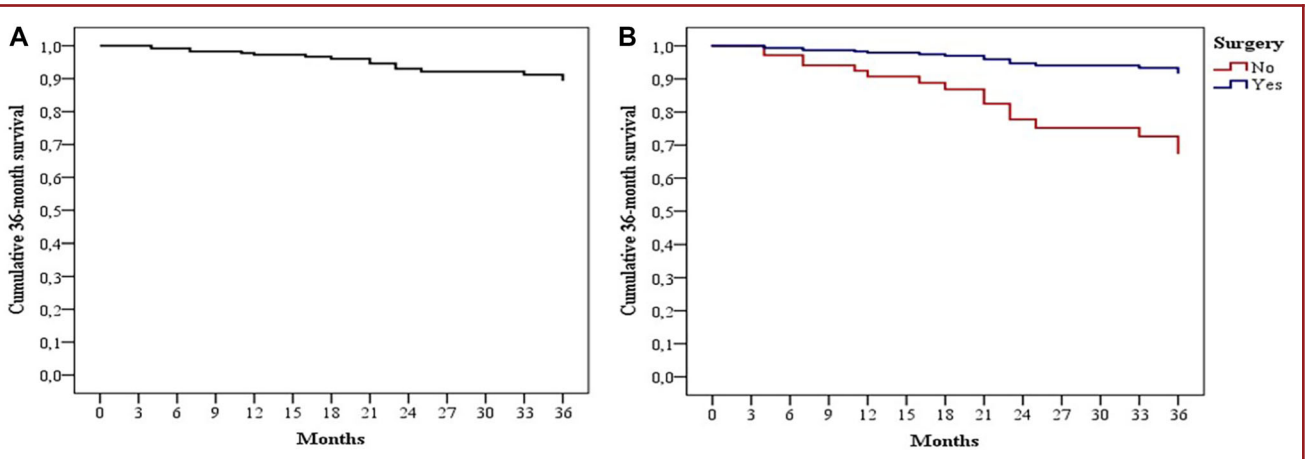


FIGURE 2. **A**, *Overall survival.* **B**, *Influence of the surgical treatment on overall survival.*

this association was not statistically significant (each additional year, HR 1.03, 95% CI 0.99-1.07, $P = .065$). The multivariable analysis was restricted to the cases with survival outcome data and since the number of patients that also lacked tumor size was low (6 patients), we decided not to perform any imputation of missing data. There was no missing age. Therefore, the final sample for the multivariable analysis was 133 patients.

DISCUSSION

The PTPR originates from a distinct ependymal cell of the subcommissural organ, which has a unique papillary architecture associated with particular histological and immunohistochemical features.[1,7,9,57,76] Although rare, a crescent number of cases have been registered over time since PTPR was first described by Jouvet et al[4] and included in the 2007 WHO classification of central nervous system tumors.[5,6] Thus, a refined histologic diagnosis criteria has been developed since its first report.[6] However, the standard of care for PTPR and its biological behavior have not yet been well established.

This systematic review evidenced an increasing number of PTPR cases over the years, with an increase of nearly 30% of cases in 5 yr (Table 1). We opted for a patient-level analysis, since case reports represented the majority of studies. As previously stated, PTPR is most prevalent in young adults with clinical presentation of a headache with signs of intracranial hypertension due to an obstructive hydrocephalus. MRI findings are nonspecific. However, they permit appreciation of the tumor size, which is shown by the multivariable analysis to be related to the survival rate at 36 mo. Surgical treatment is mandatory, as it is the only treatment modality effective for reducing mortality at 3 yr. GTR was not shown to improve outcomes in our series, as had been previously postulated. Local recurrence was a hallmark of the PTPR clinical course, and disease-free interval might have prognostic value.

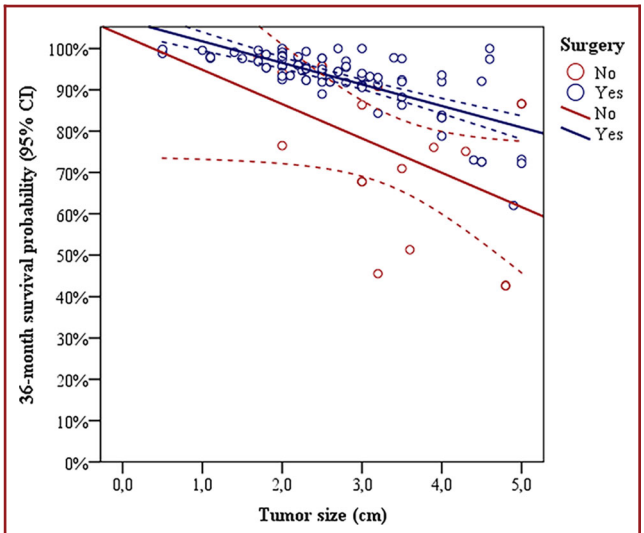


FIGURE 3. *Survival probability at 36 mo according to tumor size and surgical treatment.*

TABLE 4. Outcomes for PTPR

Variables	Total
Follow-up (median and quartiles, months)	36.0 (15.0-84.0)
Survival rate (36-mo)	116/139 (83.5%)
Functional outcome (GOS)[a]	
1	24/76 (31.6%)
2	1/76 (1.3%)
3	7/76 (9.2%)
4	23/76 (30.3%)
5	21/76 (27.6%)
Recurrence	68/118 (57.6%)
Time to recurrence (median and quartiles, months)	29.0 (10.5-45.5)

Data presented as valid n (%), except if otherwise specified.
SD: Standard deviation; GOS: Glasgow outcome scale.
[a]Functional outcome at the end of each original study follow-up.

TABLE 5. Multivariable Analysis for Predictors of 36-mo Survival

Variable	Coefficient ± SE	Wald	HR	95% CI	*P* value
Age (each yr)	0.03 ± 0.02	3.39	1.03	0.99-1.07	.065
Tumor size (each cm)	0.68 ± 0.29	5.49	1.98	1.11-3.53	.019
Surgical treatment	−1.83 ± 0.53	11.74	0.16	0.05-0.45	.001

SE: Standard error; HR: Hazard ratio; CI: Confidence interval.

Clinical and Imaging Characteristics

The PTPR has a marked clinical onset: a headache associated with clinical signs of intracranial hypertension, such as vomiting without nausea, early morning headache, and bilateral papilledema, followed by visual disturbance, characterized by diplopia and visual blurriness. These first symptoms represent warning signs that require radiological investigation. Our results showed a 2-mo median delay for tumor diagnosis after the appearance of the first symptoms. Radiological assessment depicted hydrocephalus in 88.6% of patients. An emergency procedure, such as a ventriculostomy or ventriculoperitoneal shunt, was required in nearly half of the cases. The PTPR is located deep in the brain's topography, near the mesencephalic tectal area (anteriorly-inferiorly) and the cerebral aqueduct/third ventricle (posteriorly). Even a small pineal mass can become symptomatic due to compression of these adjacent structures.

Tumor size at diagnosis had prognostic implication for PTPR in the multivariable analysis. Hydrocephalus at clinical presentation did not affect outcomes. Symptoms of increased intracranial pressure were the main reason for early diagnosis; diagnosis of this type may lead to early treatment and possibly to better outcomes. However, we did not have access to functional outcomes or cognitive evaluations at discharge, so we were unable to evaluate the implications of sudden neurologic deterioration due to acute hydrocephalus in those patients. We believe that tumor size might influence treatment response, as demonstrated in our results.

PTPR present as well-circumscribed masses and tend to be larger than other pineal tumors. On MRI, it has variable T1 and T2 signal intensities with heterogeneous contrast enhancement. A cystic component or the presence of multiple cysts was described, as well as hyperintense foci in T1-weighted images representing inclusions of proteins. Our results found those features in more than 80% of PTPRs. However, few papers reported MRI features, and those that reported these features did not show them to influence overall survival. Image patterns on diffusion-weighted image and spectroscopy have not been established in the literature on PTPRs yet.[11] In 2 case reports, spectroscopy showed increased choline and N-acetyl-aspartate and a discrete lactate peak for PTPR.[9,32,43] Differentials include teratomas, meningiomas, metastatic carcinomas, and parenchymal pineal tumors.[1,11,77]

Histopathology

Histologic examination of PTPRs reveal epithelial-like neoplasm arranged in 2 major architectural patterns, papillary and solid. Papillary areas exhibit broad fibrovascular cores, sometimes containing multiple capillaries that impart a pseudoangiomatous aspect to the tumor. These vessels are lined by a multilayered cuboidal or columnar epithelium with pale eosinophilic cytoplasm, arranged in perivascular pseudorosettes.[78,79] In solid regions of the tumor, clearing or vacuolation of the cytoplasm may occur, often containing an acidophilic intracytoplasmic structure that is periodic acid-Schiff positive. True rosettes, tubules, and canals have also been reported, and tend to be more prominent in solid areas.[19,78]

High-power examination reveals round-to-oval nuclei situated toward the basal pole of the cells. Finely mottled chromatin

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and small nucleoli may be present. Occasional nuclear features include hyperchromasia, multinucleation, and anisonucleosis, which seem to be reactive in nature.

Immunohistochemistry is an essential tool in the diagnosis of pineal region neoplasms. The expression of a wide array of low molecular weight cytokeratins appears to be the trademark of PTPR, with particularly strong reactivity to CK18. Staining for S100, NCAM, neuron-specific enolase (NSE), and transthyretin is frequent. PTPR is usually negative for GFAP, synaptophysin, chromogranin, and neural antigens, although focal, weak staining may be observed.[4,76,78,80] Mitotic rates and Ki67 immunolabeling vary widely, and correlation with biological behavior is yet to be determined. Some authors advocate that higher proliferative activity is found in younger patients.[19] Heim et al[79] have reported an association between increased mitotic/proliferative activity and higher recurrence rates in a series of 21 patients.[79] Further studies remain necessary to corroborate this data.

Electron microscopy analysis of PTPR suggests its origin is in specialized ependymal cells of the subcommissural organ. Tumor cells exhibit features of ependymal, secretory, and neuroendocrine cells. Copious cytoplasm containing zonated organelles is found in both dark and clear cells, held together by intercellular junctional complexes. A rough endoplasmic reticulum containing secretory products is a common finding, and so are numerous clear and coated vesicles, mitochondria, and microvilli.[14,76,78]

All pineal region tumors with papillary architecture and/or epithelioid cell morphology are included in the differential diagnosis of PTPR. The diffuse positivity for cytokeratins is the major difference between PTPR and other primary central nervous system lesions, except for choroid plexus papillary lesions. The latter often exhibit single-layered epithelium, Kir7.1, and stanniocalcin-1 staining, whereas PTPRs do not. Ependymomas are typically negative for CK18 and Cam5.2, although AE1/AE3 expression caused by cross-reactivity with GFAP has been reported. Papillary meningiomas may have characteristic EMA expression and should not exhibit diffuse positivity for cytokeratins. Germ cell tumors boast a distinctive morphology and immunophenotype, which includes reactivity for PLAP, AFP, CD30, and β-HCG.[7,76,78]

Detection of a pineal neoplasm with papillary architecture in an adult patient should warrant a differential with metastatic tumors. Careful review of the clinical history, morphology, and the absence of vimentin, NSE, and S100 immunoreactivity favors the diagnosis of metastatic carcinoma. Primary site markers such as TTF-1 are also helpful.[4,8,20]

This paper focused on the clinical course and treatment of PTPR to provide concise results; further studies are necessary to detail the histopathological findings of this particular tumor.

Treatment

Resection of a pineal lesion is the primary therapeutic intervention to improve outcomes and survival rate.[9,78] Resection is effective for both benign and malignant lesions. Several authors believe that gross total tumor resection is critical for preventing local recurrence.[1,9,10,19] Multivariable analysis confirmed that patients who underwent surgery presented better survival rates at 36 mo. However, GTR did not improve outcomes over other resections. The pineal region is in a deep location, surrounded by important structures of the brainstem. We encourage maximum safe surgical resection to ameliorate response to adjuvant treatments and improve survival rate. GTR might be achieved, but it entails risks that should be considered.

The infratentorial supracerebellar approach is classically employed to access the pineal region.[81,60] This approach is optimal for small or medium-sized tumors confined to the quadrigeminal cistern or third ventricle (types A, B, and C). Type D or E tumors, with large extensions to supra- and infratentorial compartments, are better treated through an occipital transtentorial approach. A combined approach has been considered in cases featuring giant tumors.[82] The infratentorial supracerebellar approach was employed most often in our series. Nevertheless, very few papers addressed the surgical approach to the PTPR in detail, and those that addressed it did not provide enough data for statistical analysis.

Other treatment modalities for PTPR include isolated or adjuvant RTx, QTx, or SRS. Brain-local radiation is a well-established treatment to avoid local recurrence of intracranial ependymomas. Although the method has been adopted by most authors in these case reports, our large series did not find better outcomes with adjuvant RTx (whole-brain or fractioned 3-dimensional conformal RTx). The use of QTx (adjuvant temozolomide and cisplatin) was reported as an alternative, especially for recurrence or evidence of cerebral spinal fluid dissemination. However, there is no evidence of better outcomes after QTx. Fauchon et al[9] studied the effectiveness of RTx and QTx in treatment of the PTPR. There was no improvement in overall survival or performance status after these treatments.

The SRS is another treatment modality that should be explored for relatively small brain tumors in deep locations. Kim et al[36] reported the first use of the gamma knife surgery for a PTPR. Although the surgery controlled the disease in the pineal region, it did not avoid leptomeningeal seeding, and the patient experienced a progressive decline in neurological status months later. Fauchon et al[9] promoted SRS as the primary and adjuvant treatments for PTPR. In this series, the patients who underwent SRS without tumor debulking developed several local recurrences. SRS employed in addition to surgical resection led to better control of local disease. Local recurrence was not considered a prognostic factor for the survival rate at 36 mo.

Univariate analysis did not show significant results for alternative treatment modalities, such as QTx, RTx, and SRS. Our nonsignificant results might be explained by the limited sample available for individual analysis of each treatment modality, heterogeneous protocols of QTx, RTx, and SRS, and bias due to the retrospective design of the study. Prospective studies with well-defined methodology are necessary to draw further conclusions, yet these may be unpractical due to the rarity of the disease.

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Biologic Behavior

The PTPR can be classified as WHO grade II or III, with a high propensity for local recurrence, such as ependymal or choroid plexus carcinomas.[58,79] A moderate mitosis rate was evidenced, with a mean Ki67 of approximately 6%. Surgical resection is the current standard of care, while PTPR's sensitivity to RTx and QTx need more convincing evidence. Studies registered long-term follow-up with relatively good functional outcomes. We found a median follow-up period of 36 mo with satisfactory GOS. More than 50% of patients had GOS 4 or 5 at the last available follow-up.

Of PTPRs, 56% showed local recurrence in follow-up. Tumor relapse did not determine a worse prognosis. However, a longer disease-free interval correlated to better overall survival results at 36 mo, according to the univariate analysis. Distant dissemination was described by Kim et al[36] in a patient with a rare leptomeningeal seeding into the internal acoustic canals, anterior clinoid process, cavernous sinuses, pituitary stalk, and optic chiasm. These lesions did not respond to SRS, and the patient had an unfavorable outcome with death 11 mo after the first symptoms were detected. Hong et al[30] reported spinal metastasis as an intradural mass at the level of L3. They assumed dissemination through cerebral spinal fluid, based on the tumor's location. This patient underwent surgery, followed by local radiation, but the patient experienced rapid neurologic deterioration and died 8 mo after detection of the spinal tumor. A complete cerebrospinal imaging investigation must be performed at the time of diagnosis and during follow-up. Distant metastatic lesions represent aggressive behavior of tumors and can lead to worse outcomes.

Limitations

Our paper is the first comprehensive multivariable analysis published with patient-level data on PTPR. Most available reports were single case descriptions or case series with small samples, but individual information could be gathered from each patient and analyzed using refined statistical tools. This retrospective design may have influenced the results presented, as it could introduce publication bias related to this type of paper. Some data have been missed due to different methodologies employed among the studies. Therefore, we have included a variable number of studies according to the topic analyzed in order to reunite the best information available. The time interval between interventions (surgery, QTx, RTx, or other) was not analyzed because this information was not available in most studies. Functional outcomes represented by the GOS were not included as endpoints because they were mostly described at the last follow-up instead of at hospital discharge immediately after treatment.

Despite these limitations, our patient-level analysis is the largest PTPR's sample in the literature, with 177 patients studied. Our results provide reasonable data for the rational management of PTPR and constitute the best evidence available thus far related to this uncommon and poorly understood neoplasm.

CONCLUSION

Our results provide consistent information related to the clinical outcomes and management of PTPR. Tumor size and surgical resection are associated with 36-mo survival. Surgical resection remains the current standard of care, as it provides the best prognosis at 36 mo. We did not find additional benefit to GTR or adjuvant treatment.

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COMMENTS

Initially described in 2003, papillary tumors of the pineal region (PTPR) are one of the most recent additions to the histopathologic milieu of lesions seen in this location. They present a significant clinical challenge as they are locally aggressive and frequently recur. While the literature is replete with case reports and small case series on these lesions, their rarity has precluded the establishment of the treatment algorithms often applied to other pineal region tumors. In this meta-analysis – the largest for PTPRs – the authors evaluate how current surgical and clinical management patterns impact patient outcomes. Most interestingly, and in contrast to several other smaller studies, the authors report that while surgical resection improved patient outcomes, gross total resection did not confer a survival benefit. Given the difficulty in obtaining a definitive diagnosis at the time of surgical resection, this result underscores the importance of maximal safe resection of pineal lesions while ensuring that enough tissue for diagnostic workup is obtained. Performing an open surgical resection and biopsy upfront certainly achieves this goal. The authors' result suggests that this may be the optimal initial surgical strategy in these patients, as opposed to a needle biopsy which may be complicated by sampling errors, low diagnostic yield, and the need for an additional surgical procedure.

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The authors should be commended for having completed the first comprehensive study regarding the presentation, treatment, and management of patients with papillary tumors of the pineal region (PTPR), a rare and poorly understood neoplasm that has only recently been classified by the WHO. Due to the rarity of the pathology, the authors were forced to rely on case reports and case series of varying quality; however, they were able to use multivariate analysis to study individual factors related to patient outcomes. Ultimately, they have determined that tumor size and surgical resection are the only two factors associated with survival at 36 months. By providing a comprehensive review of the literature for PTPR and addressing clinical presentation, surgery, the role of gross total resection, adjuvant therapy, imaging, and histopathology, the authors conclusions can be translated into reasonable recommendations that can help guide clinical decision making.

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The Emerging Role of Biomarkers in Adaptive Modulation of Clinical Brain Stimulation

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Received, July 31, 2018.
Accepted, March 1, 2019.
Published Online, April 8, 2019.

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Therapeutic brain stimulation has proven efficacious for treatment of nervous system diseases, exerting widespread influence via disease-specific neural networks. Activation or suppression of neural networks could theoretically be assessed by either clinical symptom modification (ie, tremor, rigidity, seizures) or development of specific biomarkers linked to treatment of symptomatic disease states. For example, biomarkers indicative of disease state could aid improved intraoperative localization of electrode position, optimize device efficacy or efficiency through dynamic control, and eventually serve to guide automatic adjustment of stimulation settings. Biomarkers to control either extracranial or intracranial stimulation span from continuous physiological brain activity, intermittent pathological activity, and triggered local phenomena or potentials, to wearable devices, blood flow, biochemical or cardiac signals, temperature perturbations, optical or magnetic resonance imaging changes, or optogenetic signals. The goal of this review is to update new approaches to implement control of stimulation through relevant biomarkers. Critical questions include whether adaptive systems adjusted through biomarkers can optimize efficiency and eventually efficacy, serve as inputs for stimulation adjustment, and consequently broaden our fundamental understanding of abnormal neural networks in pathologic states. Neurosurgeons are at the forefront of translating and developing biomarkers embedded within improved brain stimulation systems. Thus, criteria for developing and validating biomarkers for clinical use are important for the adaptation of device approaches into clinical practice.

KEY WORDS: Deep brain stimulation, Biomarkers, Epilepsy, Parkinson disease, Adaptive brain stimulation, Beta hypersynchrony, Phase amplitude coupling, Evoked field potentials, Closed loop

Neurosurgery 85:E430–E439, 2019 DOI:10.1093/neuros/nyz096 www.neurosurgery-online.com

Both extracranial and intracranial brain stimulation can exert influence over multiple brain areas through modulation of disease- and patient-specific neural networks.[1-4] Placement of intracranial brain stimulation and recording electrodes is currently executed via preoperative recordings and detailed imaging. In contrast, extracranial stimulation can be either diffusely applied to the skull or targeted to engage specific brain regions, such as in transcranial alternating current and transcranial magnetic stimulation (TMS),[5-7] or lie outside of the cranium, such as vagal nerve stimulation (VNS)[8] and spinal cord stimulation (SCS). Engagement of appropriate circuitry and treatment efficacy in all these forms of brain stimulation is typically verified by clinical assessment and symptom reduction as well as direct electrophysiological recordings with stimulation.

Clinical biomarkers or endpoints may also provide objective endpoints to therapy or elucidate why patients with optimal electrode position still have such variable

ABBREVIATIONS: AD, Alzheimer's disease; **aDBS,** adaptive DBS; **BCI/BMI,** brain computer/machine interface; **DBS,** Deep brain stimulation; **ECoG,** electrocorticography; **EEG,** electroencephalogram; **EMG,** electromyogram; **ECAP,** evoked compound action potential; **FOG,** freezing of gait; **GPi,** globus pallidus internus; **IPG,** internal pulse generator; **LFP,** local field potential; **PD,** Parkinson disease; **PAC,** phase amplitude coupling; **SCS,** spinal cord stimulation; **SCC,** subcallosal cingulate; **STN,** subthalamic nucleus; **TMS,** transcranial magnetic stimulation; **TBI,** traumatic brain injury; **TRD,** treatment resistant depression; **VNS,** vagal nerve stimulatorstimulation; **Vim,** ventral intermediate nucleus of the thalamus

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clinical outcomes, including development of dose-response functions.[9] The current clinical approach to programming stimulation parameters requires significant time and effort from both patient and clinician and can be subjective Use of biomarkers may facilitate objective and/or automated automatic adjustments,[10] improved power efficiency, and fewer side effects by linking both underlying physiologic network activity and symptom relief. This may be achieved through intermittent or continuous, dynamic adjustment based on amplitude- or time-dependent changes.[2,11]

Neurosurgeons have been at the forefront of concept and device testing in clinical research in brain stimulation. The number of clinical and feasibility studies, usually in small pilot groups of patients for brief time frames (hours), indicate that this is an area moving rapidly from the laboratory to the bedside and eventual standard clinical applicability.[12-16] A number of clinical trials for newly marketed and prototypical responsive, scheduled, and adaptive systems are ongoing at academic institutions. Here, we describe direct neurosurgery translation of intra- and extracranial feedback modulation of brain stimulation, updating an earlier, more comprehensive review.[2]

BIOMARKERS BY DISEASE

Characteristics of an ideal surrogate biomarker are noted in Table 1. The complexity of potential biomarkers and their barriers to implementation highlight the need for neural circuitry modeling. There are many avenues to analyze these biomarkers in initial clinical trials, ranging from intraoperative testing to verify appropriate electrode position, using percutaneous wires after surgery for short-term testing, or using one of the implanted sensing/recording devices for longer term data collection. Clinical implementation of biomarkers ranges from FDA approved devices to human trials with research devices to experimental biomarker identification pending clinical application. Table 2 provides a broad overview.

EPILEPSY

Intracranial Stimulation

Intracranial neurostimulation for medication resistant epilepsy includes the responsive NeuroPace system (NeuroPace Inc, Mountain View, California) or intermittent, scheduled stimulation via anterior thalamic (ANT) DBS (both now approved in the US – NeuroPace for responsive stimulation and ANT DBS for intermittent, open loop stimulation).[17] ANT DBS, placed via microelectrode recording and frontal lobe scalp electroencephalogram (EEG), may modulate general frontal lobe networks to reduce seizure susceptibility.[18] Scalp EEG in this setting could also be used as an intraoperative or permanent surrogate biomarker for both localization and to initiate stimulation in relation to onset of an epileptic event.[19]

The NeuroPace system is intermittently triggered by ictal events (or their precursor signatures) using detectable depth electrode or electrocorticography (ECoG) cortical ictal activity as the biomarker. Regions based on preoperative localization are stimulated to prevent seizure onset and propagation.[20,21] NeuroPace's clinical limitations include accurate localization of both of both inputs and outputs, detection of pre-ictal events sufficiently far enough in advance of a seizure so that the patients does not detect clinical symptoms, and determining exact stimulation algorithms.

Extracranial Stimulation

Extracranial stimulation includes cervical VNS, likely affecting diffuse brain networks.[8,22] Recent studies have indicated that direct electrocardiographic detection of tachycardia in the pre-ictal state may provide a key feedback signal to trigger scheduled intermittent stimulation. This signal is available since typically the internal pulse generator (IPG) for VNS is placed in the left chest region. Additionally, focused extracranial alternating current stimulation may also be activated (using intracranial sensing electrodes) to increase seizure threshold and/or treat ictal events.[7] This is a promising new approach that may be able to take advantage of temporal interference to both spatial and temporal focusing of extracranial stimulation.[5]

PARKINSON DISEASE

Although ~75% of Parkinson disease (PD) patients obtain some symptom improvement with DBS placement in the subthalamic nucleus (STN) or globus pallidus internus (GPi),[23,24] there remains considerable variation in outcomes as the pathways and pathophysiology of the disease are not currently fully understood.[25] It is possible that different biomarkers will likely be required for different PD symptoms, rather than attempting to treat the various disease phenotypes with one treatment biomarker.

Beta Band Oscillations

Spontaneous beta band oscillatory activity at 13 to 30 Hz spreads through the cortico-basal network upon synchronization of the cortex, basal ganglia, and thalamus.[25] This beta band activity thought to be a marker of PD state in animal models and humans and a possible surrogate for treatment effect for bradykinesia (not tremor).[26] Hypersynchrony lessens after therapeutic doses of dopaminergic medication and clinical levele DBS stimulation.[27] Such synchrony can be recorded from motor cortex (ie, ECoG)[28] or directly from STN or GPi DBS contacts.[29-31] Whitmer et al[25] recorded subdural cortical ECoG and spontaneous STN local field potential (LFPs) (in a clinical study of 13 humans). Several clinical studies have now shown proof of principle that adaptive adjustment of beta band oscillations may be equi-efficacious to continuous DBS and more efficient.[12,32]

Phase Amplitude Coupling

Based on primary motor cortex ECoG, de Hemptinne et al[28,33] demonstrated that DBS reduces phase amplitude coupling (PAC)

TABLE 1. General Characteristics of a Desirable Biomarker

Desired biomarker characteristic	Description
Directly correlates to clinical symptoms	Relevant in time course and extent to a measurable symptom
Constantly/dynamically tracks disease state	Dynamically changes as stimulation alters neural circuits to reflect symptom improvement
Minimal sampling error	Ability to differentiate location where best, representative signal obtained
Signal stability over time	Signal faithfully and consistently tracks disease state across multiple conditions, such as walking, sleeping and activity
Signal can be differentiated from background "noise"	The signal can be distinguished from ongoing spontaneous activity to be distinct and measurable
Confirmation of desired signal	Distinguish pathological signal from overlapping normal cortical signals
Adjustable	Ability to fine tune for patient to patient variability and across dynamic states

A biomarker must do more than simply match clinical symptoms in order to be effectively implemented in a future adaptive or closed-loop device. This table highlights keep qualities necessary to make controls implementation and device design efficacious.

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between beta oscillations and higher frequency superimposed oscillations characteristic of PD. PACs are thought to cooridinate timing between various cortical areas for execution of tasks.[34] While they are seen in normal cortical activity, the increased PAC in PD possibly reflects neurons restricted to an inflexible pattern by PD, leading to the hallmark symptoms of rigidity and bradykinesia.[33] Adaptive DBS (aDBS) using motor cortex sensing appears to be equally efficacious to continuous DBS in a few long-term patients.[12,16]

Evoked Potentials and Oscillations

In some cases, more than one DBS electrode may be needed for clinical efficacy, and an additional electrode at another anatomical site (ie, STN + GPi together) may prove to be beneficial. Instability and freezing of gait (FOG) are significant causes of morbidity in Parkinson patients.[35] There is evidence of this in a few closed-loop systems described in the literature. For example, one study utilized a closed-loop system to alter GPi stimulation based on pedunculopontine nucleus potentials (correlated with FOG and instability) as the outputs.[36] Dyskinesias after STN DBS are another application for dual electrode recordings by targeting STN together with GPi.[37,38] Dual electrodes can allow for stimulation on one electrode and recording on another, although stimulation evoked potentials can also be recorded from STN DBS electrodes alone,[39] showing an interesting resonant neural activity. Lastly, spontaneous gamma band oscillations (ie, 60-90 Hz) may also indicate hyperkinetic PD symptoms, (eg, dyskinesias) as another biomarker beyond beta band oscillations as discussed earlier.[40]

Spinal Cord Stimulation

SCS may improve gait in particular, and freezing episodes, possibly through direct activation of lower extremity circuits and/or secondarily through indirect activation of intracranial circuits.[41,42] Biomarkers derived from SCS evoked recordings (ie, from stimulating one contact and recording on other contacts) or secondary sensory stimulation evoked recordings (ie, stimulating on a SCS contact and recording from sensory cortex) may be useful to titrate the level of SCS required (ie, above or below the level of paresthesia). This is an area of early clinical investigation.

TOURETTE SYNDROME

Tourette syndrome is an idiopathic neuropsychiatric disorder defined by motor and phonic tics[43,44] and intraoperative thalamic recordings of the centromedian parafasicular complex suggest that low frequency bursts correlate with the clinical phenotype. Maling et al[44] studied 5 Tourette patients implanted with the Neuropace device localized using cortical ECoG strips, CT-MRI fusion and intraoperative microelectrode recordings to delineate their anatomic CM target. Best symptom relief from stimulation correlated with increased gamma activity and eventual return to higher thalamic frequencies. Alternatively, low frequency oscillations in the GPi that precede electromyogram (EMG)-proven tic recordings by 50 to 2000 ms may be a possible anticipatory biomarker.[13,45] Okun et al[46] demonstrated long-term efficacy of scheduled stimulation in Tourette Syndrome as compared to purely continuous stimulation. They have also reported proof of concept for responsive DBS (where the spontaneous biomarker triggers onset of stimulation) for Tourette's pathology with improved battery life.[15]

ESSENTIAL TREMOR

Ventral intermediate nucleus of the thalamus (Vim) stimulation can help to treat essential tremor.[47] Kent et al[48]

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TABLE 2. Possible Targets, Potential Surrogates, and Current Developmental Hurdles

Disease	Stimulation targets	Surrogate/biomarker	Biomarker development challenges
Epilepsy	Anterior thalamic nucleus, CM thalamus, localized seizure focus, vagal nerve	Intracranial: abnormal synchrony and excitability noted on EEG, ECoG and depth electrodes	Ability to sense pre-ictal event, validate clinical efficacy in human trials
		Extracranial: heart rate (VNS)	
Parkinson (rigidity and bradykinesia)	STN, GPi	Beta hyper synchrony (Beta band oscillations)	Direct correlation with clinical symptom improvement
		Phase amplitude coupling	Signal differentiation
Parksinon (dyskinesia)	STN + Gpi (dual electrode)	Gamma oscillations	
Parkinson (FOG)	Pedunculopontine nucleus	DBS: Increased beta frequency or cholinergic neuron action potentials	
		SCS: Spinal cord evoked recordings or secondary sensory evoked recordings	
Tourette	Centromedian nucleus of thalamus and GPi	Low frequency thalamic oscillations, cortical oscillations	Identify best control system mode (continuous versus adaptive versus responsive)
Essential tremor	Vim (of thalamus)	Internal: ECAP External: EMG, accelerometry	Signal stability over time; signal variability between patients; signal to noise ratio
Alzheimer's disease	Fornix, entorhinal cortex, hippocampus, cingulate, precuneous, frontal cortex	Electrophysiological: hippocampal evoked potentials chemical: cholinergic activity	Very theoretical, stimulation target/biomarker identification
Depression	Subcallosal cingulate (SCC) and Area 25 (medial forebrain bundle), nucleus accumbens	Imaging based: tractography intersection of 3 fiber bundles near SCC, frontal lobe evoked potentials	Leading biomarker identification

These sites summarize the disease-based discussion in the text. (CM – centromedian nucleus (of the thalamus); PET – positron emission tomography; SPECT – single photon emission computed tomography; STN – substantia nigra; EEG – electroencephalogram; ECoG – electrocorticography.)

investigated the electrical stimulation-induced evoked compound action potential (ECAP) intraoperatively arising from neural elements (likely axons) near the lead.[39] Neural activation appeared to correlate with programmatic stimulation adjustment and clinical tremor as measured by accelormeter.[49] Specifically, low frequencies near 10 Hz worsened the tremor, but high frequencies closer to 130 Hz improved it. Unfortunately, ECAP signal has significant patient-to-patient variability, as significant as an order of magnitude between subjects.[39,49] ECAP signal may also be altered over time by glial scarring, potentially hampering long-term applications.[49] One idea to improve the signal to noise ratio during Vim DBS would be to record the electrically evoked field potential with a second electrode placed anteriorly in VOP to reduce stimulation artifact.[43,48,50]

Indeed, accelerometers for dynamic tremor measurement are examples of external biomarkers from wearable devices that can potentially provide closed-loop control.[51] Cagnan et al[52] developed a prototype device coupling the measured phase of tremor to the DBS IPG for intermittent, phase - specifica stimulation. Alternatively, Basu et al[53] utilized surface EMG and accelerometry in an on/off adaptive control system incorporating a tremor-predictive algorithm.[53] Another highly innovative tremor treatment approach utilizes the typical clinical observation that patients with essential tremor have minimal to no tremor at rest. By recording and interpreting a motor cortical ECoG signal indicating pending arm motor activity, Vim DBS may dynamically control tremor prior to and during activity with less power use.[13]

ALZHEIMER'S DISEASE

It is unclear the degree to which the abnormal circuits in Alzheimer's disease (AD) may be treated or affected by stimulation.[54,55] Novel techniques such as DBS of the fornix in clinical trials have thus far shown limited efficacy.[56,57] Large hippocampal evoked potentials could potentially become biomarkers both to adjust fornix stimulation amplitude (currently empirically determined) and to estimate plasticity following fornix stimulation. Another alternative site is the nucleus basalis of Meynert,[58] although a cholinergic biomarker and associated dose-response curve might be required to titrate effectively such widespread and diffuse cholinergic enhancement.

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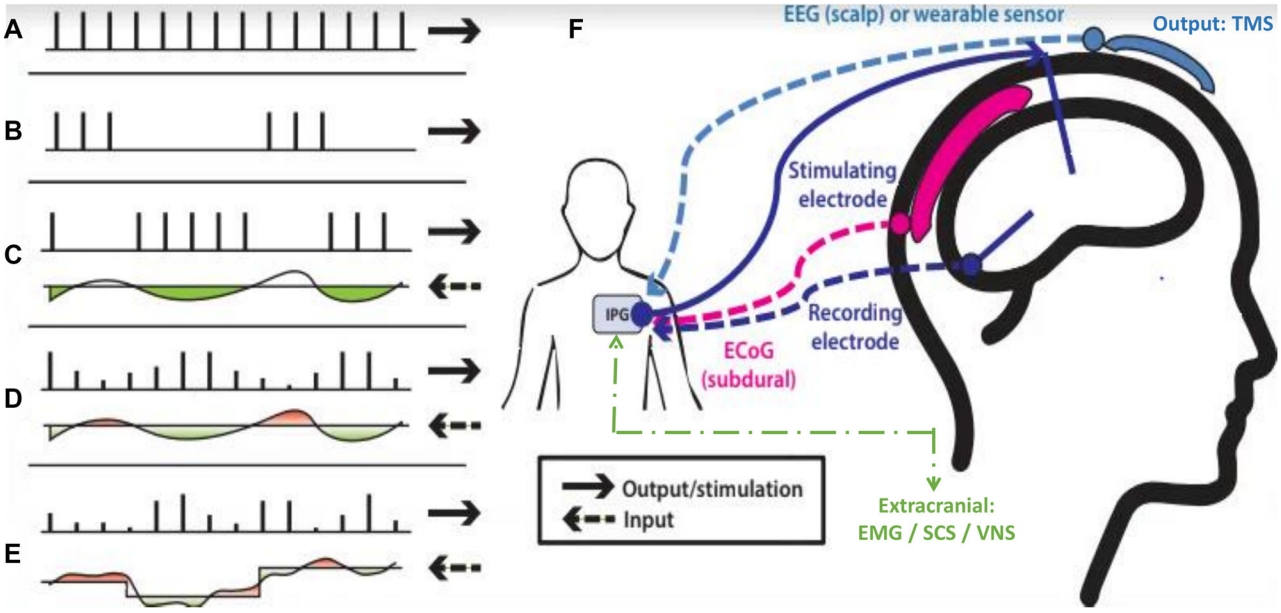


FIGURE *DBS stimulation control models show the input below each pulse sequence, reflecting continuous changes in the biomarker, and the upper reflects the actual system output in response to the input. The green color indicates stimulation on and the red color indicates stimulation off. The various modes include:* **A**, *continuous stimulation;* **B**, *scheduled intermittent stimulation;* **C**, *responsive stimulation. Each stimulation is the constant but requires a threshold to be met;* **D**, *adaptive stimulation. The number and amplitude of pulses may vary to achieve a control point value;* **E**, *closed-loop stimulation. A dynamic continuous output informs a continuous dynamic input.* **F**, *Depending on disease pathology, input may be from the DBS lead or secondary DBS, EEG, or ECoG electrodes. Output stimulation from the IPG is primarily though the DBS/parenchymal lead but future subdural or scalp hardware options are possible. Reprinted from: Hoang et al*[2] *Copyright © 2017 Hoang, Cassar, Grill and Turner. CC BY.*

Extracranial stimulation has also been implemented to improve[59-61] and potentially to forestall worsening in AD. Extracranial stimulation may demonstrate the advantage of widespread circuitry activation, matching the nearly global pathology in more advanced AD. Intracranial markers may help adjust and define a dose-response curve for extracranial stimulation.[62]

DEPRESSION

DBS for treatment resistant depression (TRD) with numerous potential sites, including but not limited to subcallosal cingulate (SCC) white matter, Brodmann area 25 gray matter, and ventral capsule/ventral striatum.[63,64] While small clinical trials have demonstrated even long-term efficacy,[65] larger industry sponsored trials such as BROADEN (St. Jude) have not.[66] Intraoperative testing is challenging as patient response is highly variable, personal, and may be delayed over weeks to months. TRD is a significant example of a disease state where nonelectrophysiologic biomarkers are the leading candidates. For example, when utilizing tractography to guide lead placement, autonomic effects (tachycardia and increases in skin conductance) correlate with intraoperative testing.[67] SCC DBS lead placement for research studies was initially anatomically guided[65] but therapeutic responses were widely variable.[68] Prospective trials instead targeting white matter tract intersections near the SCC and interrogation of these individual white matter tracts with ECoG monitoring may be promising to better guide electrode placement and long term efficacy.[69-71]

Both VNS and TMS of the left frontal lobe have also been FDA approved for treatment of depression.[72] However, a clear dose-response curve based on symptoms and intracranial responses will be critical to establish a circuitry basis for stimulation.

STIMULATION AND CONTROL MODES

Time constants are a measure of the system's response time to an input.[73] These can be significantly different. For example, tremor responses to thalamic DBS may stabilize within 10 to 20 s[74] whereas subthalamic DBS for bradykinesia may initiate within seconds but require more than 30 min to stabilize.[75] There are 5 major subtypes of systems control policy as related to

TABLE 3. Control Systems Description

Control mode	Feedback type	Description of feedback	Time constant of activation
Continuous	Clinician observation	Clinician manual adjustment	Monthly or frequency of clinic visits
Scheduled Intermittent	None	Preset stimulation amplitude turned on or off at preset timing	Preset timing determined by system physiology or empirically
Responsive	Triggered by threshold event	Preset stimulation amplitude turned on or off by trigger (with defined lockouts)	0.5-5 s, can be repeated
Adaptive	Single biomarker input, continuous monitoring	Stimulation output can be turned on or off, or scaled, for continuous adjustment	Tremor ~ 10 s Rigidity, Gait ~ 60-90 s
Closed-Loop	Multiple channels of input biomarkers for continuous analysis	Continuous prediction of brain intent for action	20-50 ms for information update

The use of biomarkers can be described in various approaches, including continuous and intermittent. Responsive and adaptive show progressively more flexibility in when to perform stimulation (ie, triggered by an event or threshold) and adaptive has inherently further flexibility in prolonged stimulation and levels of stimulation when on. Closed loop can apply to any scheme where a feedback signal is used to alter stimulation, but commonly is used in a brain-machine context. The chart gives the type of feedback which can be used, the nature of the feedback and time constants to be considered in delivering the feedback.

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stimulation (Figure and Table 3). The clinician's input decreases and system autonomy increases through the spectrum. In order of increasing complexity, the five subtypes include:

1. simple continuous (Figure A) with clinical adjustment;
2. intermittent or scheduled using a fixed schedule and fixed amplitude (Figure B), such as the 30 sec on/5 min off commonly used cycling in VNS;
3. responsive with a preset amplitude and width but requires a trigger for initiation (Figure C) from threshold changes in a few channels of input signal;
4. adaptive with flexibility of variable durations of stimulation in response to a single biomarker input threshold, or a variable amplitude (Figure D) typically set to minutes for on/off cycling;
5. closed-loop within the brain-machine interface context, this isa multidimensional input, rapid outputs from continuousprocessing of inputs (ie, 10 to 20 Hz), and appropriate feedback signal (Figure E).

In these various modes the control policy can be defined internally (ie, a state transition map embedded within the device based on contingencies) or externally.[22] Each state transition can then lead to a predefined stimulation change. Table 4 categorizes the devices and biomarkers previously described by the control subtypes discussed here.

SCHEDULED INTERMITTENT STIMULATION

Epilepsy and Parkinson Disease

Rather than continuous stimulation (ie, Figure A), ANT DBS and VNS for epilepsy implement an intermittent, scheduled stimulation at a preset level[17] (Figure B, Table 3). Scheduled intermittent stimulation or additional on-demand stimulation can reduce the amount of unnecessary stimulation and may preserve network sensitivity which can otherwise adapt or fade with constant stimulation. Phase-dependent stimulation intermittently dampens the network may critically dampen the system if the response is sufficiently rapid.[52] There are criteria for a stimulation trigger with a "lockout" or safety mechanism preventing overstimulation. The pulse repetition frequency of DBS for epilepsy is critical as EEG synchrony caused by alternative frequencies can amplify seizures.[21] The SANTE trial targeting the anterior nucleus of the thalamus (ANT) demonstrated reduction in seizure frequency, even over the long term, using scheduled, intermittent programming.[18] Specifically, SANTE randomized participants to stimulation at either at 5 V or 0 V (no stimulation) with set parameters of 90 microseconds, 145 Hz, and a 1 min "on" and 5 min "off".

Newer Medtronic DBS devices (ie, Medtronic PC + S and RC + S; Medtronic Inc, Dublin, Ireland) also feature lock-out, phase-in timing and adjustable response based on the specific input (Figure C).[76-78] The RC + S has been implemented with more advanced features than the PC + S, including built in logic for contingent, incremental stimulation changes in response to a recorded signal, as well as a distributed network which can encompass both internal and external devices.

RESPONSIVE CONTROL

Epilepsy

Certain disease processes, like epilepsy, may have long asymptomatic or unpredictable periods between events where constant stimulation programming may not be ideal.[20] The key difference from the scheduled intermittent control is the recording of

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TABLE 4. Biomarkers Classified by Control Subtypes

Control mode/class	Specific examples of biomarkers/devices	Description
Simple continuous	Open Loop DBS	All adjustments via clinician/direct patient observation
Intermittent	ANT DBS	Scheduled on preset timing, therefore no biomarkers used (exception: VNS and heart rate as biomarker preceding seizure event)
	VNS	
Responsive/triggered	Neuropace	Predetermined output in response to threshold
	DBS for tourette	Conditional output in response to motor cortex patterned responses
	DBS for essential tremor	Output in response to motor cortex movement initiation signal
Adaptive	DBS for Parkinson disease (eg, PC + S and RC + S)	Currently external; response tailored to continuous input signal.
		Includes motor cortex/STN coherence (eg, PAC), spontaneous beta band, stimulation-evoked responses.
Closed Loop	Braingate system	Multiple inputs (~100 channels) process to form contingent output
	Other custom systems	

network signals to initiate the stimulation. For the previously mentioned Neuropace system, stimulation at a preset level is delivered in a binary on/off fashion when upper or lower thresholds are reached, much as a thermostat controls a furnace.

ADAPTIVE CONTROL

Parkinson Disease

Arguably, the most advanced control systems concepts regarding brain stimulation are the last 2 types – aDBS and closed loop (Figure D and Figure E). Adaptive stimulation has adjustable or contingent stimulation in response to the external or internal biomarker, as compared to the fixed output of a responsive system. There is a growing body of evidence that aDBS is clinically feasible and safe.[12,16,32] Little et al[79,79] utilized STN aDBS via an externalized system on/off system linked to processing of LFPs (beta frequency amplitude). Notably the stimulation was dynamic with variable widths. They also compared continuous, scheduled intermittent, and adaptive systems directly and found statistically significant improvement with the adaptive system in motor scores, decreased speech side effects, reduction in stimulation time, and decreased energy utilization.[80] However, longer-term data showed that the adaptive system demonstrated much improved efficiency but only a modest improvement in efficacy.[81] Most recently, Arlotti et al[12] studied neurophysiologic and clinical responses of LFP-based aDBS for advanced Parkinson for 8 h after implantation in 2 patients. Beta-band power correlated with clinical manifestations and aDBS automatically decreased DBS amplitude during "on" states effectively while preventing dyskinesia.[12,82]

A theoretical variation called a "*scalar adaptive system*" *utilizes inputs of varying amplitudes to approach a desired set point.*[11,73] The difference between the desired set-point and the current value is noted and a larger difference generates a correspondingly larger change in stimulation, hence the term "scaled output"(Figure D). This slightly more sophisticated variation embodies classic control system principles by minimizing the amount of output oscillation and time to achieve a steady state. It also mitigates large or complete on/off changes which may cause uncomfortable side effects for the patient. A scalar response may also adapt to varying needs during task performance to dynamically control system response.

CLOSED LOOP

Motor and Psychiatric Disease

At the most complex end of the control spectrum, brain computer/machine interfaces (BCI/BMI) require constant or near-constant sensing, feedback parameter, and output for motor control.[83] Whereas adaptive stimulation may have only a single setpoint, closed-loop stimulation can utilize dynamic or multiple setpoints, adjusted with the information from the rapidly updated feedback parameter.[84]

The initial work in BCI/BMI has largely focused on motor disorders. The previously mentioned Medtronic "Activa PC + S" has been used in a number of pertinent examples such a BCI in a locked-in patient with amyotrophic lateral sclerosis.[85] More recently Widge and Sahay[86] have also proposed extensions of closed-loop theory to psychiatric applications. Early work suggests that closed-loop feedback can uniquely modify neural network firing patterns with continued exposure to BCI training. This may have unique applicability to psychiatric disease which can fluctuate or clinically change over time.[86] Additionally, a preliminary low frequency signal has been recorded in nucleus accumbens, which may be useful for measurement of impulsivity.[87]

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Adaptive Stimulation with Extracranial Stimulation

There are a number of strategies to improve and focus extracranial stimulation and to develop contingent stimulation dependent upon intracranial biomarkers.[7,8] VNS may also be contingent upon either direct patient triggering or electrocardiographic signals, such as tachycardia which may precede or accompany an aura or seizure onset.[8] In this case, the VNS may be rapidly triggered to attempt to abort a seizure at the onset or in a precursor stage.

CONCLUSION

Identifying and determining efficacy of stimulation biomarkers will require considerable additional development, mainly in collaboration with neurosurgeons who can facilitate development, clinical testing and implantation of new systems. Electrophysiological measures, neurochemical or other markers may also be reasonable options beyond current imaging and electrophysiological measures. While treatment of disease can obviously be optimized, the potential to better understand the underlying circuitry on many pathologies is a more fundamental goal of this study. It is critical at this stage to identify the most promising biomarkers into proof of concept translational work, and well-designed clinical trials to demonstrate efficacy, safety, or noninferiority in comparison to conventional devices. Neurosurgeons are the driving force in many instances to implement and improve adaptive modulation systems as well as understand the underlying clinical diseases.

Disclosures

This work was supported by NIH R01 NS079312, NIH R37 NS040984, and NIH UH3 NS103468. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Postoperative Rigid Cervical Collar Leads to Less Axial Neck Pain in the Early Stage After Open-Door Laminoplasty—A Single-Blinded Randomized Controlled Trial

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Received, April 12, 2018.
Accepted, July 11, 2018.
Published Online, August 3, 2018.

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BACKGROUND: Cervical collars are used after laminoplasty to protect the hinge opening, reduce risks of hinge fractures, and avoid spring-back phenomena. However, their use may lead to reduced range of motion and worse neck pain.

OBJECTIVE: To investigate the clinical, radiological, and functional outcomes of patients undergoing single-door laminoplasty with or without collar immobilization.

METHODS: This was a prospective, parallel, single-blinded randomized controlled trial. Patients underwent standardized single-door laminoplasty with mini-plates for cervical myelopathy and were randomly allocated into 2 groups based on the use of collar postoperatively. Clinical assessments included cervical range of motion, axial neck pain (VAS [visual analogue scale]), and objective scores (short-form 36-item, neck disability index, and modified Japanese Orthopaedic Association). All assessments were performed preoperatively and at postoperative 1, 2, 3, and 6 wk, and 3, 6, and 12 mo. Comparative analysis was performed via analysis of variance adjusted by baseline scores, sex, and age as covariates.

RESULTS: A total of 35 patients were recruited and randomized to collar use (n = 16) and without (n = 19). There were no dropouts or complications. There were no differences between groups at baseline. Subjects had comparable objective scores and range of motion at postoperative time-points. Patients without collar use had higher VAS at postoperative 1 wk (5.4 vs 3.5; $P = .038$) and 2 wk (3.5 vs 1.5; $P = .028$) but subsequently follow-up revealed no differences between the 2 groups.

CONCLUSION: The use of a rigid collar after laminoplasty leads to less axial neck pain in the first 2 wk after surgery. However, there is no additional benefit with regards to range of motion, quality of life, and complication risk.

KEY WORDS: Cervical myelopathy, Neck collar, Randomized controlled trial, Open-door laminoplasty, Plates

Neurosurgery 85:325–334, 2019 DOI:10.1093/neuros/nyy359 www.neurosurgery-online.com

The hugely popularized "open-door" technique, originally reported by Hirabayashi et al,[1] is commonly used for cervical myelopathy treatment. The opening created by this technique is historically held open by sutures but this carries risk of "spring-back" phenomenon where the lamina opening closes leading to recurrence of symptoms.[2] Recent trends in cervical laminoplasty are for the adoption of mini-plates to maintain the laminar opening.[3-7] These stronger fixation methods may avoid complications such as implant failure, hinge fracture, and the resulting spring-back deformity. These titanium plates have shown longevity due to promotion of hinge healing without much complication.[7]

There is still no consensus regarding the use of rigid cervical collar immobilization in the early postoperative period. Collars are commonly used by surgeons, especially after anterior cervical surgery to avoid instrumentation complications and to improve fusion

ABBREVIATIONS: ANCOVA, 1-way analysis of covariance; **CIs,** confidence intervals; **CT,** computed tomography; **MCID,** minimal clinically important difference; **mJOA,** modified Japanese Orthopaedic Association; **NDI,** neck disability index; **SF-36,** short-form 36-item; **VAS,** visual analogue scale

rates despite limited evidence.[8,9] For laminoplasty, their use may be helpful to protect the hinge, reduce risks of hinge fractures, and avoid spring-back phenomena. However, certain complications have been reported with rigid neck collars. Their use may reduce cervical range of motion on average by 62.9%.[10] To perform the usual functional activities of daily living, one only requires less than half of the normal cervical range of motion,[11] but with 5 d of rigid collar use, there is reduced eye movement speed and increased body swaying due to uncontrolled calf muscle vibrations.[12] Prolonged cervical movement restriction may have a detrimental effect on proprioception in both standing and movement.[12] Though the duration of neck collar use has also been attributed to postoperative axial neck pain,[13-15] Hida et al[16] suggested that there were no differences in pain and outcomes with 2-wk postoperative use of rigid neck collars after double-door laminoplasty. However, results should be interpreted with caution due to unknown sensitivity of secondary outcomes (range of motion, lordotic angle or functional scores) with a high dropout rate.

With the trend towards more rigid fixation for maintaining hinge opening, plates may preclude the need for cervical collars. This may allow for earlier mobilization, less neck stiffness, and axial neck pain, while reducing the cost for manufacturing neck collars, daily fitting, and maintenance. Ultimately, this may improve patient-reported outcomes. Hence, we aim to conduct a randomized controlled trial to investigate the clinical, radiological, and functional outcomes of patients undergoing open-door laminoplasty with or without cervical neck collar for postoperative immobilization.

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METHODS

Study Design and Participants

The study was a prospective, parallel single-blinded randomized controlled trial conducted during the study period from April 2015 to February 2018. Patient recruitment was performed at 2 tertiary referral centers by the attending spine specialist. Inclusion criteria were any male or female patient aged over 18 yr, and clinical and radiological signs compatible with cervical myelopathy undergoing open-door laminoplasty for 1 or more spinal compression levels. Patients were required to be literate and able to comprehend the study to be enrolled. Exclusion criteria included all patients with previous cervical spine surgery, congenital deformities, spine infection or inflammation, tumor, previous spinal fusion surgery, non-Chinese ethnicity, undergoing workman's compensation, and unable or refusing to follow the standardized rehabilitation protocol. All patients were given information sheets regarding the study protocol and both verbal and written informed consents were obtained at the time of recruitment. Patients were consented for a study comparing the clinical, radiological, and functional parameters with or without rigid neck collar use after single-door laminoplasty. Details regarding each study parameter were not divulged to the study participants. Ethics approval was obtained from the local institutional review board. There were no changes to the methods after trial commencement.

Randomization and Masking

Patients who fit the inclusion and exclusion criteria and agreed to participation in the study were consecutively recruited and randomized at the time of surgery to either receive a Philadelphia collar for 3 wk postoperatively or to be allowed free mobilization without any collar immobilization. Random allocation was performed using a computer program with a block size of 10. One independent investigator generated the random allocation sequence, enrolled participants, and assigned participants to interventions. It was not possible for patients and operating surgeons to be blinded to the group allocation. All assessors of clinical, radiological, and objective scores were blinded to patient details. All patients randomized to the neck collar group had the collar removed prior to assessments to maintain blinding.

Sample Size Calculation

Due to lack of previous available data comparing patients with collar immobilization after open-door laminoplasty, we performed a pilot study and periodically assessed the difference in axial neck pain (primary outcome) between the 2 groups measured by the visual analogue scale (VAS). Based on the 2-wk postoperative data for the first 20 subjects recruited, we found that a sample size of 16 patients in each group could achieve a power of >80% with a significance level of 0.05 to detect a minimal VAS difference of 1.5 as reported as the minimal clinically important difference (MCID).[17-20] Based on this, we included a total of 35 patients assuming a 10% attrition rate.

Treatment Procedure

Operative techniques were standardized and performed by 4 surgeons from the same institute. After exposure of the laminae and lateral mass adequate for plate placement, a full-thickness trough was made at the junction of laminae and lateral mass with a high-speed burr. The side chosen was based on the side with more significant clinical symptoms. On the contralateral side, another trough was created. However, this was only a partial-thickness trough made as a hinge to allow the lamina opening towards the ipsilateral side. The spinal canal was thus expanded and maintained open by titanium mini-plates at all levels. After fixation was completed, the wound was closed over a deep drain, which was kept until the 24-h blood loss was less than 50 ml. For patients allocated to the collar group, they were allowed to remove the collar temporarily whilst resting in bed. All patients were prescribed pregabalin 75 mg twice daily for the first week after surgery and allowed paracetamol 500 mg 4 times daily as needed postoperatively. For the postoperative rehabilitation protocol, all patients were allowed respiratory and circulatory exercises, transfer, and walking training as well as other activities of daily living. Patients were allowed discharge to home once independent living or carer was arranged. General home training program included exercises, postural training, and walking. Both groups were restricted from contact sports, heavy lifting, or extreme cervical spine movements within 3 mo of operation.

Study Parameters and Outcome Measures

All primary and secondary outcome measures were recorded immediate preoperatively (day before surgery), at 1, 2, 3, and 6 wk postoperatively, and at 3, 6, and 12 mo postoperatively. This was standardized and followed without any changes during the trial. A 1-yr follow-up was deemed adequate as collar use was only an early postoperative intervention with unlikely long-term influences. The primary outcome measure was reported axial neck pain by VAS. Secondary

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outcome measures were divided into clinical, radiological, and objective scores, namely short-form 36-item questionnaire (SF-36) and neck disability index (NDI).

Clinical assessments included the cervical spine range of motion measured in a standardized order: active extension, flexion, lateral flexion (right then left), and rotation (right then left). The range of motion was measured by a fluid goniometer (MIE Medical Research Ltd, Leeds, United Kingdom). The modified Japanese Orthopaedic Association (mJOA) score was measured for functional outcomes. Recovery rate was measured by the Hirabayashi method[21]: recovery rate (%) = (postoperative JOA – preoperative JOA)/(17 [full score] – preoperative JOA) × 100. All clinical assessments were performed by an independent investigator who maintained blinding.

Lateral cervical spine radiographs were obtained at each respective time-point. The anteroposterior canal diameter was measured using Wolf's method,[2,22,23] which indicates the perpendicular distance between the middle of the posterior border of the vertebral body to the anterior border of the lamina. Cervical sagittal alignment was measured at C2-7 from the lower endplate of C2 to the lower endplate of C7. All lateral radiographs were obtained in the erect position. The patient was standing with the back against a board and the shoulders relaxed. They were instructed to maintain a horizontal gaze during imaging. The focus film distance was set as 180 cm while centering at the angle of the mandible. The exposure was 62-peak-kilovoltage and 8 to 10 milliamperage-seconds of x-ray energy. All images were assessed by three independent readers who maintained blinding. When the difference in measurements was less than 1 mm or 5 degrees, the mean of the 3 measurements were recorded. If there was a discrepancy of more than 1 mm or 5 degrees, a joint concluded value for reporting was decided based on consensus between the readers. Inter- and intrarater reliability analyses were performed for the radiographic measurements via intraclass correlation coefficient. The second round of reliability measurements were performed 1 mo after the first round of measurements.

Any complications including perioperative events, surgical site infections, postlaminoplasty C5 palsy, and reoperations were recorded. Radiographs were assessed for fracture or loosening of implants, and spring-back as determined by >1 mm loss of initial anteroposterior canal diameter expansion.[22]

Statistical Analysis

Due to the multiple covariates and time-points, 1-way analysis of covariance (ANCOVA) was conducted for assessing whether the collar and without-collar groups were statistically different having adjusted for covariates. Data were presented by mean scores ± standard deviation unless stated otherwise. Statistical significance was tested at 5% level for all tests. Intention to treat principle was used for continuous and discrete data. As alluded to in the sample size calculation, post-hoc analysis was performed with G*Power (version 3.0.10, Heinrich Heine University, Dusseldorf, Germany) to determine whether difference in axial VAS between groups achieved adequate power of >80%. Ninety-five percent confidence intervals (95% CIs) were reported when appropriate. Post-hoc power analysis (Cohen effect size) was used to assess the sensitivity for secondary parameters.

RESULTS

A total of 35 patients with mean age of 64.9 ± 11.4 yr at surgery were consecutively recruited and randomized to collar use (n = 16) and without collar immobilization (n = 19). Figure 1 shows the flow diagram of patient enrollment and follow-up. The first patient was enrolled on April 2015, and the last 1-yr follow-up assessment was performed on February 2018. There were neither dropouts nor complications. All subjects were analyzed by all primary and secondary outcomes. Preoperatively, both groups (Table 1) were comparable with no differences in age, VAS, range of motion, cervical spine alignment, canal diameter, or outcome scores. The inter- and intrarater reliability were good (Table 2). Sensitivities for outcome parameters are listed in Table 3.

The mean absolute and change in VAS are listed in Table 4. There was statistically significant lower mean VAS for the collar group at postoperative 1 (3.5 ± 2.0 vs 5.4 ± 2.5, $P = .038$), 2 (1.5 ± 1.4 vs 3.5 ± 2.4, $P = .028$), and 3 (1.3 ± 1.0 vs 2.8 ± 1.9, $P = .031$) wk (Figure 2). Significant reductions in postoperative VAS compared to preoperative VAS were observed only at postoperative 1 (0.8 ± 2.4 vs 3.8 ± 3.5, $P = .016$), and 2 (–0.9 ± 3.4 vs 1.8 ± 3.2, $P = .004$) wk for the collar group. There were no differences at postoperative 3-wk to 12-mo follow-up assessments.

Regarding the outcome measures, subjects had comparable NDI scores (Table 5) between groups. Patients with collar use appeared to have fewer limitations and bodily pain subscores ($P = .032$) of SF-36 (Table 6) than those without collar use. However, these differences were only in the immediate postoperative period, and did not affect the overall physical and mental component summaries. There were overall gradual improvements in mJOA (Table 7) from preoperative to postoperative 12-mo follow-up. Similar findings were observed for the recovery rate (Figure 3).

From the one-way ANCOVA analysis, there were no differences in the adjusted mean spinal canal diameter between the 2 groups (Table 8). Based on the absolute canal widening at postoperative 1 wk, there were no significant losses in canal expansion suggesting no spring-back phenomena. The cervical alignment was preserved in both groups and was consistent throughout follow-up.

Both groups recorded similar cervical range of motion (Table 9) at all follow-up assessments, except for the larger range of rotation at right side for the without-collar group at postoperative 3-wk ($P = .046$). Limitations of extension, flexion, lateral flexion, and rotation were observed within the first 2 wk postoperatively for both groups. There were gradual improvements observed up till postoperative 6 wk and were consistent beyond that.

DISCUSSION

This study assessed whether rigid cervical collar immobilization in the early postoperative period for open-door laminoplasty is necessary. Previously, there was no evidence to support the use of neck collars after open-door laminoplasty. Establishing all the

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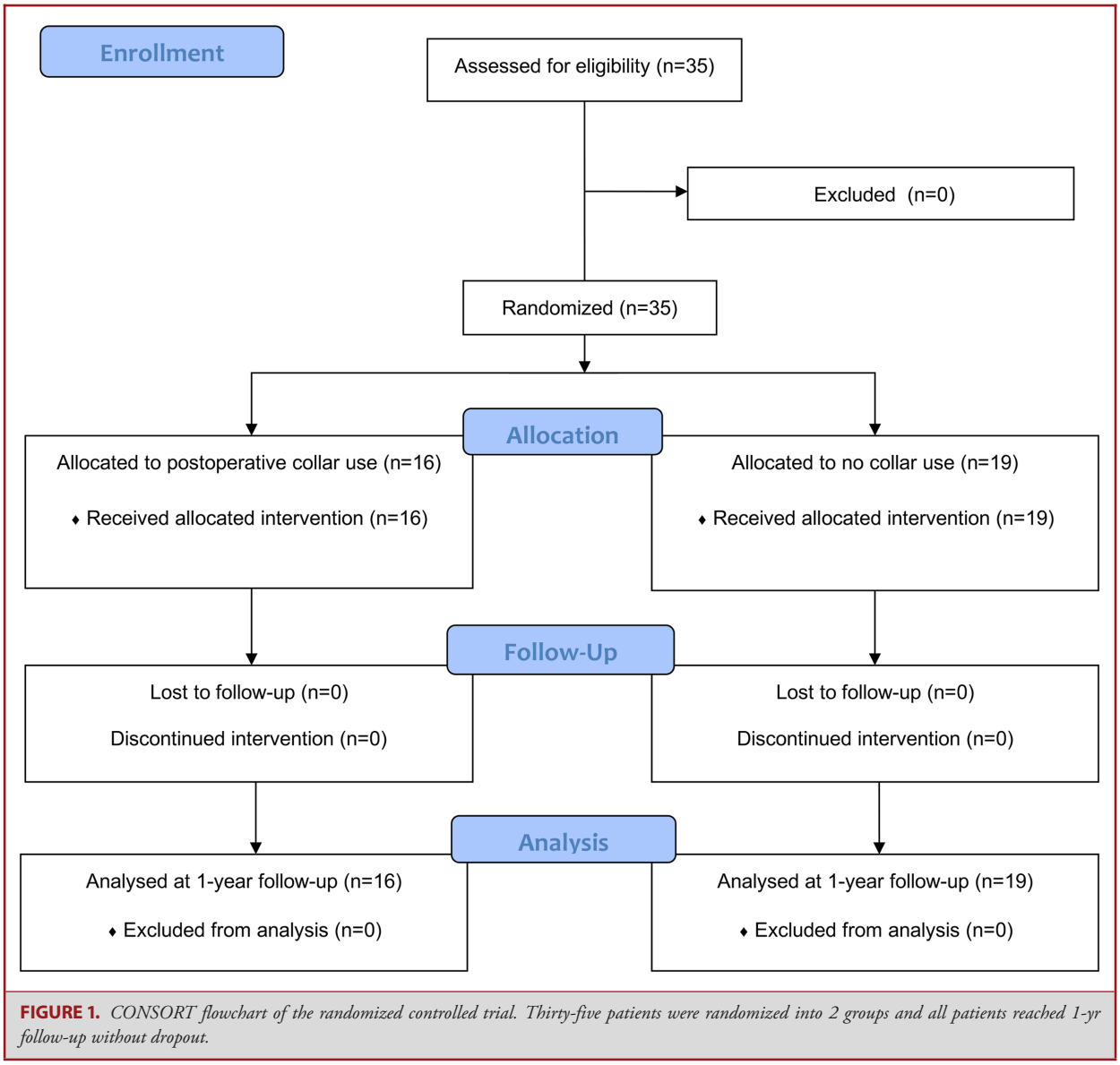


FIGURE 1. *CONSORT flowchart of the randomized controlled trial. Thirty-five patients were randomized into 2 groups and all patients reached 1-yr follow-up without dropout.*

benefits of collar use is necessary to improve our postoperative recovery protocols. Results from our study suggest that collar immobilization reduces the severity of early postoperative axial neck pain. However, due to limited differences in overall patient-reported outcomes and no reduced complication rate, the authors suggest that postoperative collar use should only be recommended for patients for concerns of postoperative axial neck pain, and not be strictly enforced.

Based on the VAS assessments, benefits of postoperative rigid cervical neck collar use are limited to reduced axial neck pain within the initial 2 wk after surgery. Beyond 2 wk, the VAS between both groups was similar. Although the VAS was also significantly lower for the collar group at postoperative week 3, the difference did not reach MCID and was considered not clinically relevant.[17-20] There was a 2-3-point lower VAS on average with collar immobilization consistent until postoperative week 2. From postoperative week 3 to 1 yr, there were no differences between the 2 groups. It is likely that the use of postoperative collars may help patients cope with the initial postoperative pain and disability. Furthermore, resisting excessive neck mobilization may aid with wound pain, which typically recovers by the end of postoperative week 2.

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TABLE 1. Baseline Demographics and Comparison of Study Groups

Parameters	Whole study population	Cervical-collar group	Without cervical-collar group	*P*-value
Number (n, %)	35	16 (45.7)	19 (54.3)	–
Male:female	20:15	10:5	10:10	–
Age at surgery (yr, ±SD)	64.9 ± 11.4	61.7 ± 14.3	67.2 ± 8.4	.199
Clinical parameters				
Axial neck pain VAS (0-10)	2.3 ± 2.2	2.9 ± 0.7	2.6 ± 2.6	.298
Cervical range of motion (degrees, ±SD)				
Extension	47.8 ± 13.8	44.1 ± 14.1	50.6 ± 13.2	.172
Flexion	55.0 ± 15.3	55.5 ± 12.1	54.6 ± 17.6	.871
Lateral—right	36.3 ± 11.1	35.4 ± 8.0	37.1 ± 13.0	.669
—Left	35.4 ± 12.7	34.9 ± 11.3	35.9 ± 13.9	.824
Rotation—right	59.1 ± 14.9	59.1 ± 15.9	59.1 ± 14.6	.995
—Left	57.1 ± 14.4	54.7 ± 14.8	58.9 ± 14.1	.410
Radiological parameters				
Cervical spine alignment—Cobb angle (degree, mean ± SD)	10.2 ± 11.4	8.0 ± 11.8	12.1 ± 11	.299
Spinal canal diameter (mm, mean ± SD)				
C3	13.6 ± 2.1	13.3 ± 1.6	13.9 ± 2.6	.458
C4	12.5 ± 2.2	12.1 ± 1.7	11.8 ± 3.6	.729
C5	12.0 ± 2.0	11.5 ± 1.5	12.5 ± 2.3	.159
C6	11.5 ± 2.4	11.3 ± 2.0	11.8 ± 2.8	.586
C7	10.7 ± 2.7	11.0 ± 2.9	10.6 ± 2.6	.701

SD, standard deviation; VAS, visual analogue scale

TABLE 2. Overall Inter- and Intrarater Reliability

Interrater reliability	95% CI	Intrarater reliability		95% CI
0.89	0.79-0.94	Rater 1	0.96	0.95-0.98
		Rater 2	0.82	0.75-0.88
		Rater 3	0.80	0.70-0.86

TABLE 3. Sensitivities for Outcome Parameters

Primary outcome	Cohen's D effect size (d), 95% CI	Secondary outcomes	Cohen's D effect size (d), 95% CI
VAS	1.02, 0.72-1.32	Canal diameter	1.43, 1.01-1.85
		NDI	0.99, 0.70-1.28
		Spinal alignment	0.66, 0.47-0.85
		mJOA	0.15, 0.11-0.19
		SF-36 PCS	0.47, 0.33-0.61
		SF-36 MCS	0.19, 0.13-0.25
		ROM	0.28, 0.20-0.36

VAS, visual analogue scale for axial neck pain; NDI, neck disability index; mJOA, modified Japanese Orthopaedic Association score; SF-36 PCS, short-form 36-item questionnaire physical component summary; SF-36 MCS, short-form 36-item questionnaire mental component summary; ROM, cervical range of motion.
Values based on the power of 82% obtained for VAS.
Cohen's D: large effect size (d = 0.8), medium effect size (d = 0.5), small effect size (d = 0.2).

TABLE 4. Comparison of Postoperative Axial Neck Pain

Time-point	VAS (mean ± SD) Cervical-collar group	VAS (mean ± SD) Without cervical-collar group	*P*-value
Preoperative	2.7 ± 2.7	2.1 ± 1.9	.659
Postoperative 1-wk	3.5 ± 2.0	5.4 ± 2.5	.038*
Postoperative 2-wk	1.5 ± 1.4	3.5 ± 2.4	.028*
Postoperative 3-wk	1.3 ± 1.0	2.8 ± 1.9	.031*
Postoperative 6-wk	0.9 ± 0.9	1.9 ± 1.7	.139
Postoperative 3-mo	1.4 ± 1.6	1.6 ± 1.8	.873
Postoperative 6-mo	1.3 ± 1.8	1.3 ± 1.5	.811
Postoperative 12-mo	1.1 ± 1.7	1.7 ± 2.4	.607
Change of VAS score with preoperative VAS as reference			
Postoperative 1-wk	0.8 ± 2.4	3.8 ± 3.5	.023*
Postoperative 2-wk	−0.9 ± 3.4	1.8 ± 3.2	.046*
Postoperative 3-wk	−1.2 ± 2.8	1.1 ± 2.6	.148
Postoperative 6-wk	−2.0 ± 2.9	−0.5 ± 2.6	.125
Postoperative 3-mo	−1.1 ± 2.5	−0.5 ± 2.4	.630
Postoperative 6-mo	−1.5 ± 3.0	−0.8 ± 2.3	.918
Postoperative 12-mo	−1.8 ± 3.2	−0.5 ± 3.1	.430

VAS, visual analogue scale; SD, standard deviation.
*denotes statistical significance ($P < .05$).

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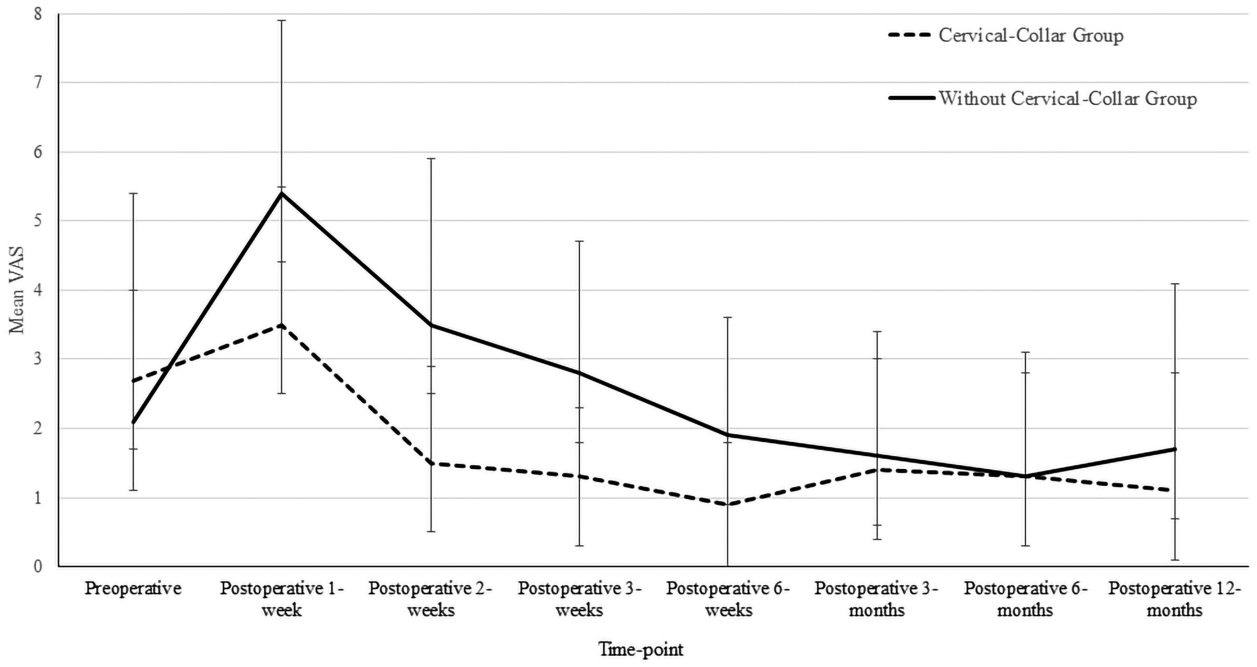


FIGURE 2. *Mean VAS with standard deviation bars at each follow-up. There was less axial neck pain for the cervical collar group as compared to no collar group at early postoperative period.*

TABLE 5. Comparison of NDI Scores

Time-point	NDI (expressed as %, mean ± SD) Cervical-collar group	Without cervical-collar group	*P*-value
Preoperative	31.8 ± 16.9	31.0 ± 11.0	.931
Postoperative 1-wk	34.2 ± 17.7	44.5 ± 11.2	.252
Postoperative 2-wk	32.0 ± 15.9	47.0 ± 14.4	.094
Postoperative 3-wk	28.4 ± 19.5	33.1 ± 14.0	.573
Postoperative 6-wk	24.8 ± 10.0	34.0 ± 9.5	.147
Postoperative 3-mo	22.5 ± 18.1	22.8 ± 7.7	.796
Postoperative 6-mo	22.4 ± 18.3	23.1 ± 12.5	.608
Postoperative 12-mo	20.8 ± 18.0	22.9 ± 10.7	.695

NDI, neck disability index; SD, standard deviation.

Although there were observed differences in axial neck pain VAS and bodily pain (SF-36 subscale) between the 2 study groups, this did not translate into detectable differences in patient-perceived outcomes via NDI and SF-36 (both physical and mental component summary scores). The bodily pain component scores were superior in the neck collar group in the first 3 postoperative weeks and were only balanced at the postoperative 6 wk reading. The absence of such impact on the overall physical and mental component summaries suggest that pain was not the predominant clinical symptom driving satisfaction after surgery. Perhaps the improvements in myelopathy were far more impactful to their health perception. This is a drawback of utilizing general health questionnaires as compared to disease specific questionnaires.

It was crucial to determine if there were any differences in clinical and radiological outcomes for efficacy and safety concerns. Both groups observed gradual improvements postoperatively from 1 wk to 1 yr in mJOA (mean 3.8) and recovery rate (54%), which is similar to previous reports.[24-26] This is to be expected as collar use should not impact the rate of improvement in myelopathic symptoms and hence despite a small effect size, it should not be an important secondary outcome to consider for differentiating the 2 groups. Despite having no patients requiring reoperation, spring-back is a concern for patients undergoing laminoplasty due to the renarrowing of the spinal canal and diminished symptomatic relief. Traditionally, spring-back has a reported rate of 10% if stay sutures are used to hold open the laminae.[2] By comparison, mini-plates provide more rigid fixation,[27,28] and our measured canal sizes suggest that spring-back does not occur in plated levels even without postoperative immobilization. In addition, no differences in cervical alignment suggest that collar use does not aid the maintenance of lordotic posture.

TABLE 6. Comparison of Short-Form 36-item Questionnaire Scores

Time-point	Preoperative		Postop 1-wk		Postop 2-wk		Postop 3-wk		Postop 6-wk		Postop 3-mo		Postop 6-mo		Postop 12-mo	
	Collar	No collar	Collar	No collar	Collar	No collar	Collar	No collar	Collar	No collar	Collar	No collar	Collar	No collar	Collar	No collar
Subscale																
Physical functioning	32.7 ± 21.8	43.3 ± 32.4	26.3 ± 26.5	28.8 ± 22.7	37.5 ± 33.4	32.6 ± 23.7	41.1 ± 32.9	44.7 ± 25.0	53.6 ± 28.3	47.2 ± 26.3	51.7 ± 26.7	47.4 ± 27.4	54.5 ± 30.0	54.1 ± 25.1	64.6* ± 18.4	50.6* ± 25.4
Role limitations due to physical health	6.8 ± 16.2	12.5 ± 31.1	13.3 ± 28.1	13.2 ± 33.2	16.1 ± 31.9	7.4 ± 24.6	25.0 ± 40.8	6.9 ± 24.0	23.2 ± 38.6	11.1 ± 28.7	25.0 ± 40.1	7.4 ± 24.6	22.7 ± 28.4	25.0 ± 35.4	25.0 ± 40.8	32.4 ± 41.2
Role limitations due to emotional problems	36.4 ± 45.8	47.2 ± 50.2	26.7 ± 38.2	27.5 ± 41.2	31.0 ± 40.2	27.5 ± 31.7	35.9 ± 46.1	29.6 ± 41.0	42.9 ± 47.9	33.3 ± 44.3	40.0 ± 40.2	33.3 ± 45.6	21.2 ± 37.3	43.1 ± 46.8	43.6 ± 45.9	52.9 ± 47.2
Vitality	39.5 ± 21.7	38.3 ± 24.2	48.7 ± 16.6	44.1 ± 15.0	56.8 ± 23.7	43.5 ± 16.5	51.5 ± 19.5	48.1 ± 17.9	50.0 ± 22.2	53.1 ± 16.1	50.0 ± 21.2	52.1 ± 22.1	44.5 ± 25.6	55.3 ± 22.7	49.2 ± 27.5	56.2 ± 16.3
Mental health	54.5 ± 28.7	67.7 ± 20.7	58.7 ± 14.5	57.2 ± 18.4	67.1 ± 25.3	62.8 ± 16.5	67.1 ± 22.0	67.7 ± 20.7	65.1 ± 25.1	68.9 ± 12.8	64.0 ± 20.8	65.2 ± 14.9	62.9 ± 20.3	71.5 ± 10.6	74.8 ± 20.7	70.8 ± 16.5
Social functioning	40.9 ± 30.2	52.1 ± 26.0	50.0 ± 32.0	47.8 ± 30.1	51.8 ± 33.9	46.3 ± 26.4	51.0 ± 32.9	50.0 ± 23.9	62.5 ± 29.4	57.6 ± 27.5	55.0 ± 25.4	63.2 ± 26.3	52.3 ± 26.1	69.9 ± 23.4	76.9 ± 19.7	66.9 ± 26.1
Bodily pain	42.2 ± 26.2	47.1 ± 22.1	44.9 ± 17.2	34.9 ± 19.0	54.9* ± 26.9	34.5* ± 23.3	52.5 ± 23.6	43.1 ± 16.4	52.0 ± 21.0	51.7 ± 17.7	54.1 ± 28.4	60.3 ± 25.4	54.1 ± 26.5	56.6 ± 20.5	61.4 ± 32.9	62.8 ± 24.5
General health perception	39.6 ± 16.4	43.3 ± 20.8	48.1 ± 18.6	43.6 ± 16.3	53.9 ± 22.3	47.8 ± 14.2	48.8 ± 20.2	51.9 ± 16.3	47.8 ± 18.9	55.0 ± 19.2	47.2 ± 21.0	54.0 ± 24.4	44.6 ± 25.5	53.4 ± 21.4	50.9 ± 25.4	53.0 ± 17.9
Physical component summary	28.8 ± 5.8	30.4 ± 9.5	29.6 ± 7.9	28.3 ± 6.4	32.6 ± 12.3	27.8 ± 7.8	33.2 ± 12.9	31.4 ± 6.8	35.2 ± 10.8	33.2 ± 7.8	35.5 ± 10.2	34.5 ± 7.7	36.3 ± 9.8	36.0 ± 9.0	39.0 ± 98	36.7 ± 9.2
Mental component summary	41.7 ± 11.7	46.1 ± 11.4	43.4 ± 8.4	42.9 ± 8.7	45.7 ± 10.0	43.9 ± 8.7	45.4 ± 9.7	43.8 ± 9.1	45.8 ± 11.5	46.1 ± 9.7	44.5 ± 8.3	45.2 ± 9.8	41.0* ± 10.0	48.3* ± 8.4	48.3 ± 11.2	48.9 ± 9.0

Data represented as mean ± standard deviation.
*denotes statistical significance ($P < .05$)

TABLE 7. Comparison of mJOA Scores

Time-point	mJOA (mean ± SD)		*P*-value
	Cervical-collar group	Without cervical-collar group	
Preoperative	9.8 ± 4.0	10.7 ± 3.0	.610
Postoperative 1-wk	11.7 ± 2.6	12.1 ± 2.9	.706
Postoperative 2-wk	11.9 ± 3.2	12.3 ± 2.2	.970
Postoperative 3-wk	12.5 ± 2.7	12.5 ± 2.2	.794
Postoperative 6-wk	13.8 ± 1.5	13.3 ± 1.9	.613
Postoperative 3-mo	14.0 ± 1.4	13.8 ± 1.6	.798
Postoperative 6-mo	13.8 ± 1.3	14.0 ± 2.0	1.000
Postoperative 12 mo	14.1 ± 1.4	14.5 ± 1.8	.636

mJOA, modified Japanese Orthopaedic Association; SD, standard deviation.

One of the advantages of not immobilizing the cervical spine postoperatively is to allow for early range of motion exercises. Furthermore, the use of rigid cervical neck collars has been shown to reduce the usual cervical range of motion by 62.9%.[10] Yet, both study groups had comparably reduced extension, flexion, lateral flexion, and rotation in the early postoperative period before returning to near normal range at postoperative 3 wk. Although right rotation for the without-collar group appeared to normalize quicker at postoperative 3 wk, there was lack of early or late follow-up differences seen in the 2 study groups. This suggests that a period of immobilization does not restrict overall range of motion. Rather, early restrictions may be a result of postoperative pain and adjustments to disability. Having a collar may not assist recovery of the posterior musculature that is injured as part of the laminoplasty surgery.[29] Nevertheless, our effect size for range of motion was small and thus may need to be addressed in a larger study.

Limitations

An important limitation of this study is the placebo effect undoubtedly present due to the study design. Since patients were informed that this was a study comparing the outcomes with or without neck collar use, study subjects using collars may experience a placebo effect. In contrast, patients not using collars may feel insecure with a perceived unstable cervical spine. Despite not disclosing the exact outcome parameters under study, patient reported measures may very well be affected by such perceptions. An ideal study design would comprise of blinding patients to the reason for this study. Different durations of postoperative immobilization may have additional influences on outcome scores. For this study, we avoided introducing another confounding element by utilizing a standardized 3-wk immobilization protocol. Further trials comparing shorter or longer duration immobilization should be performed to study these effects. Although multiple objective scores were utilized in this study, the Japanese Orthopaedic Association

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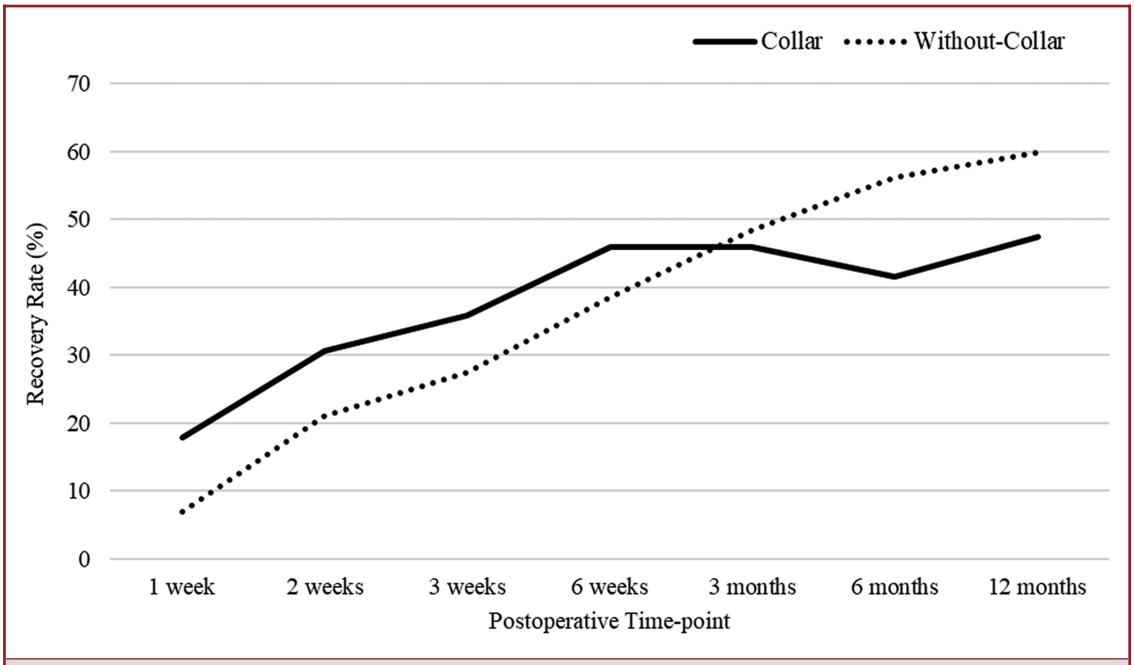


FIGURE 3. *Postoperative recovery rates (%) at each follow-up. The recovery rates were comparable from postoperative 1 wk to postoperative 12 mo.*

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Cervical Myelopathy Evaluation Questionnaire is an important patient-perceived health-related quality of life score that should be applied in these outcome comparisons as it includes not only domains of the original JOA score but also patient-perceived health status.[30-32] It is also a disease-specific questionnaire that may identify subtle changes in targeted treatment groups. Regarding the canal measurements, while a well-established radiological method was utilized in this study to identify spring-back complications, the lateral cervical radiographs may not be as sensitive as computed tomography (CT). Nevertheless, we found no differences using a randomized study design and radiographs are much more readily available and with significantly less radiation exposure as compared with CT.

Generalizability

This randomized controlled trial provided level I evidence for the benefits of early postoperative axial neck pain reduction with rigid neck collar use after single-door laminoplasty. These findings should be generalizable with standardized treatment protocols and objective assessments. Our study was adequately powered for this primary outcome with sensitivity tested to be sufficient for canal diameter measurements and NDI, both of which are key secondary outcomes of safety and efficacy, respectively. This is the era where health economics greatly influences the direction of healthcare. It is thus crucial for healthcare providers to select the most cost-effective management strategies. Despite better reported axial neck pain with collar use, limited benefits are observed in other parameters both in the early postoperative period and at longer follow-up. Hence, surgeons must consider carefully whether the additional costs of a neck collar after surgery is worth the small clinical benefits.

CONCLUSION

Many postoperative management protocols consider the use of rigid cervical neck collars after laminoplasty to avoid implant failure, loss of correction, and recurrence of neurological deficit due to perceived risk of spring-back. With modern rigid plating fixation, the risk of such complications is low. Via a randomized controlled trial, we determined that postoperative collar use in the first 2 wk after surgery leads to reduced axial neck pain. However, this difference in pain response does not impact the overall quality of life of patients. Hence, the authors recommend a temporary 2-wk use of rigid neck collars postoperatively to patients for better pain relief, but strict adherence is not necessary as limited benefits are observed elsewhere with no difference in long-term outcomes.

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TABLE 8. Comparison of Adjusted Means of Spinal Canal Diameter Measurements

Level	Adjusted means of spinal canal diameter ± SE (mm)		*P*-value
	Cervical-collar group	Without Cervical-collar group	
Postoperative 1-wk			
C3	18.9 ± 0.5	19.5 ± 0.5	.272
C4	17.6 ± 0.5	18.6 ± 0.4	.138
C5	18.2 ± 0.6	18.2 ± 0.6	.998
C6	17.1 ± 0.6	17.8 ± 0.4	.321
C7	13.1 ± 0.9	13.7 ± 0.8	.580
Postoperative 2-wk			
C3	18.8 ± 0.3	19.1 ± 0.3	.457
C4	18.2 ± 0.2	17.8 ± 0.2	.198
C5	17.8 ± 0.3	18.3 ± 0.2	.177
C6	16.9 ± 0.3	17.3 ± 0.3	.392
C7	12.8 ± 0.5	12.4 ± 0.4	.542
Postoperative 3-wk			
C3	19.2 ± 0.4	19.0 ± 0.3	.730
C4	17.8 ± 0.3	17.6 ± 0.3	.726
C5	17.3 ± 0.4	18.0 ± 0.4	.212
C6	16.3 ± 0.5	17.0 ± 0.5	.303
C7	11.3 ± 0.6	11.6 ± 0.5	.661
Postoperative 6-wk			
C3	19.2 ± 0.3	18.7 ± 0.2	.182
C4	18.1 ± 0.3	17.4 ± 0.3	.159
C5	17.3 ± 0.5	18.1 ± 0.5	.265
C6	16.5 ± 0.5	17.1 ± 0.5	.439
C7	12.8 ± 0.7	13.1 ± 0.7	.771
Postoperative 3-mo			
C3	18.8 ± 0.3	19.2 ± 0.3	.387
C4	17.6 ± 0.3	17.8 ± 0.3	.753
C5	16.8 ± 0.4	18.0 ± 0.4	.061
C6	16.6 ± 0.4	17.0 ± 0.4	.472
C7	12.8 ± 0.6	13.0 ± 0.5	.852
Postoperative 6-mo			
C3	18.6 ± 0.3	18.4 ± 0.3	.656
C4	17.8 ± 0.3	16.8 ± 0.3	.038
C5	17.4 ± 0.5	16.9 ± 0.4	.465
C6	16.6 ± 0.6	16.0 ± 0.5	.459
C7	12.7 ± 0.5	12.5 ± 0.4	.765
Postoperative 12-mo			
C3	17.9 ± 0.4	18.0 ± 0.3	.844
C4	17.3 ± 0.3	16.9 ± 0.3	.444
C5	16.7 ± 0.5	17.4 ± 0.4	.273
C6	16.6 ± 0.5	16.1 ± 0.4	.487
C7	13.0 ± 0.6	13.5 ± 0.5	.520

SE, standard error.

TABLE 9. Comparison of Cervical Range of Motion

	Cervical range of motion (degrees, mean ± SD)		
	Cervical-collar group	Without cervical-collar group	*P*-value
Preoperative			
Extension	43.9 ± 13.6	51.0 ± 54.5	.095
Flexion	55.5 ± 11.7	54.5 ± 18.0	.909
Lateral—right	35.4 ± 7.8	37.2 ± 13.4	.883
—Left	34.9 ± 10.9	35.9 ± 14.3	.832
Rotation—right	58.9 ± 15.4	59.3 ± 14.9	.909
—Left	54.1 ± 14.5	59.6 ± 14.1	.271
Postop 1-wk			
Extension	34.4 ± 14.8	32.9 ± 15.9	.832
Flexion	24.5 ± 10.0	26.3 ± 14.1	.909
Lateral—right	26.8 ± 10.8	26.4 ± 11.6	.806
—Left	22.7 ± 9.1	25.9 ± 13.3	.481
Rotation—right	41.8 ± 14.0	45.1 ± 17.7	.523
—Left	42.9 ± 15.7	46.9 ± 18.0	.403
Postop 2-wk			
Extension	43.1 ± 15.3	42.3 ± 15.2	.987
Flexion	29.1 ± 9.4	34.8 ± 12.9	.161
Lateral—right	29.8 ± 7.5	28.6 ± 8.0	.806
—Left	27.5 ± 8.7	28.0 ± 9.5	.883
Rotation—right	48.9 ± 10.8	49.7 ± 12.9	.731
—Left	51.0 ± 16.2	52.6 ± 16.7	.731
Postop 3-wk			
Extension	47.3 ± 14.4	48.6 ± 11.8	.528
Flexion	42.0 ± 10.5	44.5 ± 12.4	.484
Lateral—right	38.4 ± 7.5	34.8 ± 6.0	.073
—Left	33.1 ± 10.1	32.8 ± 12.0	.851
Rotation—right	50.9 ± 10.2	56.0 ± 14.6	.046*
—Left	56.2 ± 12.5	59.4 ± 16.2	.443
Postop 6-wk			
Extension	54.4 ± 13.4	50.4 ± 12.3	.403
Flexion	51.6 ± 7.9	51.8 ± 12.8	.707
Lateral—right	40.9 ± 10.2	35.4 ± 9.9	.088
—Left	35.3 ± 11.5	36.2 ± 10.8	.422
Rotation—right	59.4 ± 12.2	61.6 ± 11.2	.621
—Left	63.7 ± 13.6	64.8 ± 13.2	.806
Postop 3-mo			
Extension	52.5 ± 19.5	55.1 ± 12.9	.973
Flexion	48.9 ± 10.8	50.1 ± 12.2	.679
Lateral—right	40.2 ± 8.8	38.2 ± 7.8	.529
—Left	39.1 ± 8.5	36.2 ± 9.3	.397
Rotation—right	61.4 ± 10.0	63.0 ± 9.2	.553
—Left	63.4 ± 10.6	62.8 ± 13.5	.788
Postop 6-mo			
Extension	58.5 ± 18.4	58.8 ± 15.4	.707
Flexion	47.7 ± 16.0	53.3 ± 8.6	.502
Lateral—right	40.3 ± 9.8	39.1 ± 11.5	.864
—Left	36.3 ± 10.2	39.7 ± 11.2	.430
Rotation—right	59.7 ± 8.4	63.3 ± 10.3	.319
—Left	61.0 ± 8.1	65.2 ± 8.9	.202
Postop 12-mo			
Extension	59.6 ± 12.7	57.7 ± 14.8	.683
Flexion	49.1 ± 11.3	51.9 ± 7.0	.367
Lateral—right	37.2 ± 9.3	39.8 ± 9.3	.286
—Left	34.0 ± 9.4	38.4 ± 9.7	.193
Rotation—right	59.4 ± 11.2	61.6 ± 11.6	.781
—Left	64.4 ± 9.9	66.2 ± 10.8	.545

SD, standard deviation.
*denotes statistical significance ($P < .05$).

Disclosures

This study was supported by the Health and Medical Research Fund Ref #13142371. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors performed a prospective randomized study examining the effect of rigid collars on neck pain following laminoplasty and found that, in the first 2 weeks post-op, rigid immobilization decreases neck pain. Overall, this was a reasonably well-designed study with interesting results that should be of interest to the readership. I have 1 methodological concern. It is well-known that placebo effects can account for differences in surgical outcomes. Since the patients were informed that this was a study regarding the effect of rigid collars on outcomes, those who got the brace are predisposed to placebo effects that might mitigate some of their pain while those who did not get the brace are more likely to assume that they have an unstable spine that would have done better in a brace. An ideal study design would have blinded the patients to the actual reason for the study, which is a standard methodology where there are no ethical issues involved, as in this investigation. The authors have addressed this concern in the Discussion section. Given their findings, surgeons and patients can opt to use a rigid collar or increase the use of analgesics during the first 2 weeks postoperatively, since there were no long-term differences between the 2 groups.

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Loss of BCAT1 Expression is a Sensitive Marker for IDH-Mutant Diffuse Glioma

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Received, January 30, 2018.
Accepted, June 25, 2018.
Published Online, August 3, 2018.

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BACKGROUND: *IDH* mutation is an important prognostic factor of diffuse astrocytomas. Although the majority of *IDH* mutations could be identified by immunohistochemical (IHC) stain for R132H-mutant IDH1, DNA sequencing would be required for IHC negative cases to determine their *IDH* mutation status. This approach is not cost-effective for tumors with low *IDH* mutation rates.

OBJECTIVE: To investigate whether BCAT1 could be used as a surrogate marker for *IDH* mutations, because BCAT1 is an enzyme related to *IDH* genes.

METHODS: A group of 120 anaplastic astrocytomas were immunostained for BCAT1, ATRX, and R132H-mutant IDH1. Staining results correlated with the results of DNA sequencing of *IDH1/IDH2*.

RESULTS: DNA sequencing showed *IDH1/2* mutations in 50.8% of cases of which 73.8% had *IDH1* R132H mutation. Several *IDH1* noncodon 132 mutations, ie, G97D, S122N, G123E, I130K, and G131S, which had uncertain prognostic significance, were identified. IHC stain for R132H-mutant IDH1 identified 93.3% of *IDH1* R132H mutations and 70.5% of all *IDH* mutations. BCAT1 loss was seen in 65.8% of cases, its sensitivity to identify *IDH* mutations was 96.7%. The sensitivity reached 100% for *IDH1* codon 132 and *IDH2* codon 172 mutations.

CONCLUSION: Positive BCAT1 stain could be used to exclude diffuse gliomas with *IDH1* codon 132 and *IDH2* codon 172 mutations. Selecting cases with negative BCAT1 and R132H-mutant IDH1 staining for DNA sequencing of *IDH1/2* genes could improve the cost-effectiveness of detecting *IDH* mutations particularly in tumors with low *IDH* mutation rates, and confine the need of 1p/19q assay in IDH-mutant tumors.

KEY WORDS: Anaplastic astrocytoma, BCAT1, IDH, Prognosis, Sensitivity, Specificity

Neurosurgery 85:335–342, 2019 DOI:10.1093/neuros/nyy338 www.neurosurgery-online.com

The 2016 WHO classification of Tumors of the Central Nervous System incorporates isocitrate dehydrogenase (IDH) gene mutation status into the classification of diffuse astrocytic tumors. Diffuse astrocytoma (DA), anaplastic astrocytoma (AA), and glioblastoma (GBM) are currently subclassified into IDH-mutant, IDH-wildtype, and NOS categories.[1] *IDH* mutations of these tumors involves isoforms *IDH1* and *IDH2*. Molecularly, *IDH1/2* mutations usually affect a single codon and rarely occur concurrently.[2] About 95% of all *IDH1/2* mutations are in *IDH1*, of which 85%–90% are type R132H.[3,4] Currently, if no mutation is identified at *IDH1* codon 132 and *IDH2* codon 172, the astrocytic tumor is classified as IDH-wildtype.[1] Tumors whose *IDH* mutation statuses are not fully assessed are subclassified into the NOS category.

IDH1/2 mutations play a critical role and are early events in the development of gliomas.[5] The *IDH1/2* mutation rates in DA, AA, and primary GBM are 59%–90%, 28%–82%, and 5%–10%, respectively.[5-8] They are also important prognostic factors for the higher

ABBREVIATIONS: AA, anaplastic astrocytoma; **AML,** acute myeloid leukemia; **ATRX,** alpha-thalassemia/mental retardation syndrome X-linked; **BCAT1,** branched-chain amino acid transaminase 1; **DA,** diffuse astrocytoma; **DNTs,** dysembryoplastic neuroepithelial tumors; **GBM,** glioblastoma; **IDH,** isocitrate dehydrogenase; **IHC,** immunohistochemical; **OS,** overall survival; **PA,** pilocytic astrocytomas; **PFS,** progression-free survival; **PXA,** pleomorphic xanthoastrocytoma; **TMA,** tissue microarray

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grade tumors, AA and GBM, as the prognosis of the IDH-mutant tumors was better than that of the IDH-wildtype ones.[7,9] This has also been proven in our previous study of GBMs that *IDH1* R132H mutation was a significant prognostic factor in multivariate analyses ($P = .010$).[10] The prognostic significance of *IDH1/2* mutations in DAs was controversial.[7,11]

Methods commonly used for detection of *IDH* mutations include DNA sequencing and immunohistochemical (IHC) staining using mutation-specific antibodies. As mutation-specific antibody for R132H-mutant IDH1 (Dianova, Hamburg, Germany, clone H09) had a very high sensitivity,[12] and could detect 89%–93% of *IDH1* mutations[12,13] and 81% of *IDH1/2* mutations,[4] the use of DNA sequencing was only needed for cases with negative IHC result.[1,4] In tumors that had a relatively low *IDH1* mutation rate, such as primary GBMs, the use of DNA sequencing for cases with negative R132H-mutant IDH1 IHC could still be substantial.[4]

Alpha-thalassemia/mental retardation syndrome X-linked (ATRX) encodes an essential chromatin-binding protein, and *ATRX* mutations may induce an abnormal telomere maintenance mechanism.[1,14] It is used for diffuse glioma lineage stratification, especially for some oligodendrogliomas showing astrocytoma morphology.[4] Loss of ATRX expression is mainly restricted to IDH-mutant tumors and is regarded as a hallmark of astrocytic tumors with a favorable prognosis.[15] As ATRX loss is only present in 86% of grades II and III diffuse gliomas with *IDH1/2* mutations,[16] searching for other surrogate markers with a higher sensitivity for *IDH* mutations is needed.

IDH1 mutation is associated with changes in cellular metabolism, which includes decreased branched-chain amino acid transaminase 1 (BCAT1) activity.[17,18] The latter is an enzyme, which is essential for cell growth and disease progression.[17-19] In a study of BCAT1 in GBM patients, high BCAT1 expression was associated with a high cerebral blood volume and poor prognosis.[19] It has also been shown that expression of BCAT1 was exclusive to diffuse gliomas carrying wildtype *IDH1* and *IDH2* genes.[17] Because loss of BCAT1 expression was correlated with *IDH* mutations, we hypothesized that BCAT1 loss could be used as a surrogate marker for *IDH* mutations. As for primary GBM, which has a very low *IDH* mutation rate (5%–10%), BCAT1 positivity could effectively identify the IDH-wildtype ones. It would substantially reduce the need or increase the cost-effectiveness of DNA sequencing.

In order to evaluate whether BCAT1 IHC staining could truly work as hypothesized, in this study, we correlated the IHC results of BCAT1 and R132H-mutant IDH1 stains with the results of DNA sequencing of *IDH1/IDH2* in a group of AAs. The survival of AA patients with different *IDH1/2* genotypes was also analyzed. The reason for not studying GBM was as aforementioned that its *IDH1/2* mutation rate was low, and it would need a large cohort for the study. As for AAs, its *IDH1/2* mutation rate was 28%–82%,[5-8] which would make it a better subject to study or analyze.

METHODS

Patient Selection

The study protocol was approved by our Institutional Review Board; the requirement to obtain signed consent form for study participation was waived. One hundred twenty patients with AA from 1983 to 2010 were retrieved from the Biobank of our institute. There was no 1p/19q co-deletion in any of these tumors by fluorescent in situ hybridization.

Variables

The clinical information of the patients, including age, gender, date of surgery, extent of resection, and history of medication was collected from the medical records. Tumor progression according to the Macdonald criteria was defined as 25% or more increase in size of enhancing tumor or any new tumor on magnetic resonance imaging.[20] The original histopathology slides of each patient were reviewed and appropriate tumor areas were selected for the following analyses.

Tissue Microarray Construction

Tumor samples, which were adequate for building tissue arrays with 2 mm tissue cylinders from 2 representative areas of the tumors, were selected to construct tissue microarrays (TMAs).

IHC Study

TMA sections were immunostained using R132H-mutant IDH1 specific antibody (clone H09, dilution 1:100; Dianova, Hamburg, Germany), ATRX antibody (rabbit polyclonal, dilution 1:500, Sigma-Aldrich, St. Louis, Missouri), and BCAT1 antibody (clone 51/ECA39, dilution 1:500; BD Biosciences, Franklin Lakes, New Jersey) on BOND-MAX immunostainer (Leica Microsystems, Wetzlar, Germany). On-board heat-induced antigen retrieval was performed in Bond Epitope Retrieval 1 (citrate based, pH 6.0, for IDH1 H09) and Bond Epitope Retrieval 2 (EDTA based, pH 9.0, for ATRX and BCAT1) solutions for 20 min at 100°C. The primary antibodies were incubated for 30 min (for IDH1 H09 and ATRX) or 60 min (for BCAT1) at room temperature. A VBS refine polymer detection system (Leica Microsystems) was used for visualization. All sections were counterstained with hematoxylin.

A previously proven *IDH1* R132H-mutant astrocytoma was used as positive control. Normal brain tissue was used as negative control. Strong/moderate cytoplasmic staining of the majority (>50%) of tumor cells was interpreted as IDH1 H09 positive. Only nuclear staining of ATRX was evaluated, and cases with more than 10% tumor cells with nuclear staining were recorded positive. Endothelial cells, neurons, and inflammatory cells, which generally showed nuclear staining, served as internal positive controls. Cases with no nuclear staining of the tumor cells and of their internal positive controls were excluded from this study. Positive BCAT1 staining (BCAT1+) was defined as cytoplasmic and nuclear staining in tumor cells (Figure 1A), while negative BCAT1 staining was defined as loss of cytoplasmic and nuclear staining in >10% of tumor cells (Figure 1B). Microglia or histiocytes were positive for BCAT1, which could serve as internal positive controls. Negative BCAT1 staining of the endothelial cells could serve as an internal negative control. Normal brain and germinal centers of tonsil were used as external positive control. Small lymphocytes in the tonsil were used as external negative control. All slides were read independently by 3 of the authors (D.M.H., Y.Y.C., and C.Y.H.) without the clinical information. All the discordant cases and the equivocal cases were reviewed by these three authors using a multiheaded microscope to reach a consensus and a conclusive result.

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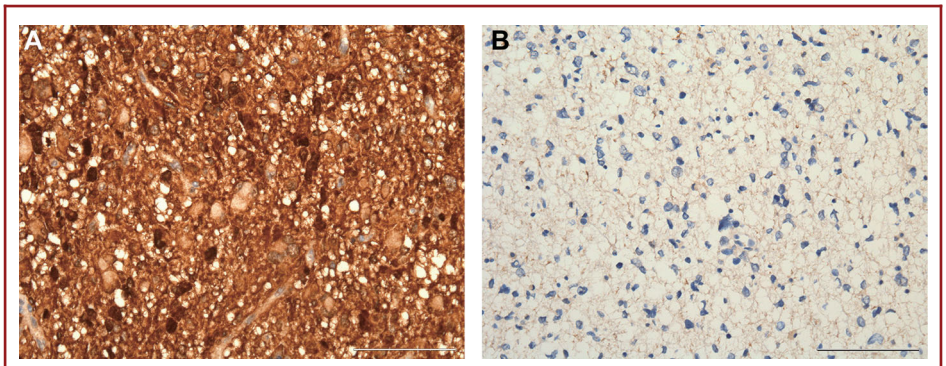


FIGURE 1. *Examples of BCAT1 IHC staining.* **A**, *An IDH-wildtype AA showing positive BCAT1 staining. Tumor cells show both cytoplasmic and nuclear staining. Negative BCAT1 staining of the endothelial cells could be used as internal negative control.* **B**, *An IDH2 R172K-mutant AA showing loss of BCAT1 expression. Scale bars = 100 μm.*

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Complete agreement among initial readings for BCAT1 IHC was 95.8% (115/120).

PCR Amplification and Direct Sequencing of *IDH1* and *IDH2*

PicoPure DNA extraction kit (Applied Biosystems, Foster City, California) was used to isolate genomic DNA from paraffin-embedded tissue. The catalytic domain region of *IDH1*, including codon 132, and of *IDH2*, including codon 172, were amplified by PCR with the annealing temperature at 60°C. Primers for PCR amplification were as follows: *IDH1* sense primer 5′-GTTGGCGTCAAATGTGCCAC-3′ and reverse primer 5′-GCCAACATGACTTACTTGATCC-3′; *IDH2* sense primer 5′-AGCCCATCATCTGCAAAAAC-3′ and reverse primer 5′-CTAGGCGAGGAGCTCCAGT-3′. Briefly, a PCR reaction containing 0.2 μM dNTP, 2 mM Mg^{2+}, 1X Amplitaq Gold buffer (Applied Biosystems), 1U of AmpliTaq Gold DNA Polymerase (Applied Biosystems) as well as primer pairs was mixed in a volume of 25 μl. The thermocycler condition was 95°C for 5 min, 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 1 min, and a final extension step at 72°C for 7 min. The PCR products were analyzed by 2% agarose gel electrophoresis. Sanger sequencing was performed using the Genetic Analyzer 310 (Applied Biosystems). The results were analyzed by Mutation Surveyor software V3.00 (Soft-Genetics, State College, Pennsylvania).

Validation Set

For validation, IHC stains for BCAT1 and IDH1 H09 were performed on TMAs containing 75 glioblastomas, 49 grade II/grade III diffuse gliomas with oligodendroglioma-like morphology, 35 pilocytic astrocytomas (PAs), 3 pleomorphic xanthoastrocytomas (PXAs), and 5 dysembryoplastic neuroepithelial tumors (DNTs). PAs, PXAs, and DNTs were included in the validation set because the majority of them were not associated *IDH* mutations. Genomic DNAs were isolated from original tumor blocks, and *IDH1/2* sequencing were performed in all cases with BCAT1–/IDH1 H09– staining result. In addition, 16 GBMs and 3 PAs were selected at random from the BCAT1 + group for *IDH1/2* sequencing.

Statistical Analysis

The Fisher's exact test or chi square test was performed for the comparison of categorical variables. Mann–Whitney or Kruskal–Wallis test was used to compare the differences in continuous variables. Progression-free survival (PFS) was calculated from the date of surgery to the date of progression. Overall survival (OS) was defined as the time from the date of surgery to the date of death or last follow-up. Survival curves were plotted by Kaplan–Meier method, and log-rank test was used to compare their differences. Multivariate Cox regression was performed to adjust for age, gender, KPS, extent of resection, bevacizumab and temozolomide treatment. Two-tailed $P < .05$ was considered statistically significant.

RESULTS

Clinical Features of the Study Cohort

Age, gender, temozolomide treatment, and bevacizumab treatment were not significantly different among patients with different *IDH1/2* genotypes. The only exception was the gross total resection rate, of which the *IDH2*-mutant cases (2/5, 40%) were significantly fewer than the *IDH1*-mutant (56/56, 100%) and *IDH*-wildtype cases (51/59, 86.4%; Table S1 in **Supplemental Digital Content**). A flow diagram describes the study cohort undergo the following tests is plotted in Figure S1 in **Supplemental Digital Content.**

DNA Sequencing of *IDH1/2* Mutations

Sequence analysis of *IDH1/2* genes revealed mutations in 50.8% (61/120) of cases, of which, 91.8% (56/61) was *IDH1*-mutant and 8.2% (5/61) was *IDH2*-mutant (Table 1 and Table S2 in **Supplemental Digital Content**). *IDH1* mutation was mostly in codon 132, of which R132H was the most common one (45/61, 73.8%). The other mutation sites were in codons 123, 97, 122 130, and 131. *IDH2* mutations were all in codon 172.

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TABLE 1. DNA Sequencing Results of *IDH1/2* Mutation of 120 Anaplastic Astrocytomas and Their Correlations With IDH1 H09 and BCAT1 IHC Staining Results

		IDH1-mutant								*IDH2*-mutant		
	Case	R132H	R132C	R132L	G123E	G97D	S122N	I130K	G131S	R172K	R172W	Wildtype
Total	120	45	3	2	2	1	1	1	1	4	1	59
IDH1 H09+	44	42	0	0	0	0	1	0	0	0	0	1
IDH1 H09–	76	3	3	2	2	1	0	1	1	4	1	58
ATRX–	32	21	0	1		0	1	0	0	3	1	5
ATRX+	60	12	1	1		1	0	1	1	0	0	43
BCAT1–	67	45	3	2	2	0	1	1	0	4	1	8
BCAT1+	53	0	0	0	0	1	0	0	1	0	0	51

TABLE 2. The Sensitivities and Specificities of R132H-Mutant IDH1 (IDH1 H09) and BCAT1 Immunostains

	Sensitivity [95% CI]	Specificity [95% CI]
All *IDH1/2* mutations		
IDH1 H09+	70.5% (43/61) [57.3–81.1]	98.3% (58/59) [89.7–99.9]
ATRX–	61.4% (27/44) [45.5–75.6]	89.6% (43/48) [77.3–96.5]
BCAT1–	96.7% (59/61) [88.7.3–99.6]	86.4% (51/59) [75.0–94.0]
Canonical *IDH1/2* mutations[a]		
IDH1 H09+	76.4% (42/55) [63.0–86.8]	96.9% (63/65) [89.3–99.6]
ATRX–	65.0% (26/40) [48.3–79.4]	88.5% (46/52) [76.6–95.7]
BCAT1–	100% (55/55) [93.5–100.0]	81.5% (53/65) [70.0–90.1]
IDH1 R132H mutation		
IDH1 H09+	93.3% (42/45) [81.7–98.6]	97.3% (73/75) [90.7–99.7]
ATRX–	63.6% (21/33) [45.1–79.6]	81.4% (48/59) [69.1–91.3]
BCAT1–	100% (45/45) [92.1–100.0]	70.7% (53/75) [59.0–80.6]
IDH1 non-R132H and *IDH2* mutations		
IDH1 H09+	6.3% (1/16) [0.2–30.2]	58.7% (61/104) [48.6–68.2]
ATRX–	54.6% (6/11) [23.4–83.3]	67.9% (55/81) [56.6–77.9]
BCAT1–	87.5% (14/16) [61.7–98.5]	49.0% (51/104) [39.1–59.0]

[a] *IDH1* codon 132 and *IDH2* codon 172 mutations.

Correlation of DNA Sequencing With IHC Results of R132H-Mutant IDH1 (IDH1 H09)

IHC staining for R132H-mutant protein (IDH1 H09) was positive in 44 cases (36.7%; 44/120), of which 43 were *IDH1*-mutant tumors (42 were R132H; one was S122N), while one was *IDH*-wildtype tumor (Figure S2 in **Supplemental Digital Content**). In terms of identification of *IDH* mutations, the IDH1 H09 IHC stain identified 70.5% (43/61) of cases with *IDH1/2* mutations, and 93.3% (42/45) of cases with *IDH1* R132H mutation. IHC staining using whole tissue sections from the original blocks of the 3 IHC negative tumors that had *IDH1* R132H mutation by sequencing were performed, and the negative staining results were confirmed. The specificities of IDH1H09 IHC staining for *IDH1/2* mutations and *IDH1* R132H mutation were 98.3% (58/59) and 97.3% (73/75), respectively (Table 2).

Correlation of DNA Sequencing With IHC Results of ATRX

ATRX staining could be evaluated in 92 cases of which positive internal control was observed. Loss of ATRX staining was noted in 34.8% (32/92) of AAs, of which 84.4% (27/32) had *IDH1/2* mutations (Table 1). Seventeen *IDH*-mutant tumors, of which 12 were *IDH1* R132H mutant and 5 were *IDH1* non-R132H mutant, retained ATRX expression. The sensitivity and specificity of loss of ATRX staining to identify *IDH1/2* mutations were 61.4% (27/44) and 89.6% (43/48), respectively (Table 2). The sensitivity of ATRX loss in detecting *IDH1* non-R132H and *IDH2* mutations was 54.5% (6/11).

Correlation of DNA Sequencing With IHC Results of BCAT1

Positive BCAT1 staining was noted in 44.2% (53/120) of AAs, and except for two cases that had *IDH1* non-p.R132 mutations,

TABLE 3. Multivariate Survival Analyses Stratified by *IDH1/2* Genotypes

Status of *IDH* genes	n (%)	Progression-free survival		Overall survival	
		Median (mo)	Hazard ratio[a] (*P*)	Median (mo)	Hazard ratio[a] (*P*)
IDH-wildtype	59 (49.2%)	9.8	1	15.8	1
IDH1-R132H mutant	45 (37.5%)	31.8	0.475 (.001)	58.6	0.412 (<.001)
IDH1-R132 variants[b]	5 (4.2%)	30.2	0.401 (.082)	30.2	0.441 (.122)
IDH1-non-p.R132 mutant[c]	6 (5.0%)	14.0	0.922 (.853)	15.3	1.262 (.629)
IDH2-mutant	5 (4.2%)	13.7	0.484 (.177)	26.5	0.739 (.548)

[a]The influences of age, sex, extent of resection, temozolomide treatment, and bevacizumab treatment were adjusted.
[b]Including R132C (3 cases) and R132L (2 cases).
[c]Including G123E (2 cases), G97D (1 case), S122N (1 case), I130K (1 case), and G131S (1 case).

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they were all *IDH*-wildtype tumors. Seven (5.8%) cases showed equivocal BCAT1 staining results (Figure S3 in **Supplemental Digital Content**), of which 1 had *IDH1* R132H mutation and 1 had R132L mutation. For analysis, the equivocal BCAT1 staining cases were grouped with the BCAT1 negative cases. Of the 67 BCAT1 negative cases, 88.1% (59/67) had *IDH1/2* mutations, and 11.9% (8/67) were *IDH*-wildtype (Figure S2 in **Supplemental Digital Content**). The sensitivity of loss of BCAT1 staining to identify *IDH1/2* mutations was 96.7% (59/61), and it reached 100% (55/55) for canonical *IDH1/2* mutations (*IDH1* codon 132 and *IDH2* codon 172) (Table 2). The sensitivity of BCAT1 loss in detecting *IDH1* non-R132H and *IDH2* mutations was 87.5% (14/16). As BCAT1 loss was noted in 8 *IDH*-wildtype AAs, the specificity of BCAT1 staining for *IDH1/2* mutations was 86.4% (Table 2).

Survival Analysis Grouped by DNA Sequencing Results

Patients with *IDH1* R132H-mutant AA had longer PFS and OS than those with *IDH*-wildtype AA (Figure S4 in **Supplemental Digital Content**). The hazard ratio of patients with *IDH1* R132H-mutant AA was significantly smaller than that of patients with *IDH*-wildtype AA in multivariate analysis (Table 3). Smaller hazard ratios were also observed in patients with other *IDH1* codon 132 (p.R132) mutations and patients with *IDH2* mutation, however, they did not reach statistical significance.

There was no significant prognostic impact of non-p.R132 *IDH1* mutations. The median OS and hazard ratio of these cases were close to those with *IDH*-wildtype.

Survival Analysis Grouped by IHC Results

As all of the IDH1 H09 + cases showed BCAT1– and all these patients received gross total resection (Table S3 in **Supplemental Digital Content**), multivariate survival analyses with adjustment of age, sex, extent of resection, temozolomide treatment, and bevacizumab treatment showed that IDH1 H09 positivity, ATRX loss, and BCAT1 loss were significant prognostic factors (Table S4 in **Supplemental Digital Content**).

Validation

Of the 75 GBMs (Table S5 in **Supplemental Digital Content**), *IDH1/2* sequencing was performed in all BCAT1–/IDH1 H09– (n = 11) tumors and 16 randomly selected BCAT1 + /IDH1 H09– tumors. There was no *IDH1/2* mutation in any of these cases.

Of the 49 diffuse gliomas with oligodendroglioma-like morphology (Table S6 in **Supplemental Digital Content**), *IDH1/2* sequencing was performed in all BCAT1–/IDH1 H09– (n = 10) cases, 3 BCAT1–/IDH1 H09 + cases, and 1 case with equivocal BCAT1/IDH1 H09 staining. *IDH1* mutation was noted in 6 cases, of which 5 were R132H and 1 was A134G. For the one *IDH1* R132H-mutant tumor with BCAT1–/IDH1 H09– IHC result in TMA, IDH1 H09 negativity was confirmed using whole tissue sections from the original block. Except for the case with equivocal BCAT1 staining, which could be due to the protein quality of the specimen, the BCAT1 staining result of all these IDH1-mutant tumors were negative.

Of the PAs (35 cases), PXAs (3 cases), and DNTs (5 cases) studied, except for 5 PAs that were BCAT1–/IDH1 H09–, the rest of them were BCAT1+/IDH1 H09– (Table S7 in **Supplemental Digital Content**). DNA sequencing of the 5 BCAT1–/IDH1 H09– PAs and 3 randomly selected BCAT1+/IDH1 H09– PAs showed no IDH1/2 mutation.

DISCUSSION

The sensitivity of IDH1 H09 IHC staining for *IDH1* R132H mutation was 93.3% (42/45) in the current study, which was similar to those reported in the previous studies (97.6%–100%).[12,13] However, its sensitivity for *IDH1/2* mutations was only 70.5% (43/61), which was lower than that of previously reported (81%).[4] The reason for the latter could be due to differences of *IDH1* non-R132H mutation rates in different study cohorts. The current study showed that BCAT1 IHC staining could help identifying *IDH1* R132H-mutant tumors that were missed by IDH1 H09 staining, and tumors with other *IDH1/2*

mutations. Indeed, the three *IDH1* R132H-mutant AAs and one *IDH1* R132H-mutant tumor in the validation set that were identified by sequencing but stained negative for IDH1 H09 were picked up by BCAT1 IHC stain (IHC stain negative).

The specificity of IDH1 H09 IHC staining for *IDH1* R132H mutation was 97.3% (73/75) that was similar to those reported previously (76.9%–100%).[12,13] False-positive staining of IDH1 H09 was noted in one *IDH1* S122N-mutant AA and one *IDH1* wildtype AA, and both stained negative for BCAT1. The discordance could be due to cross-reactivity of antibody, or the amount of tumor cells with *IDH1* R132H mutation was too small to be detected by direct sequencing.

Limitations

As this is a retrospective study, it could be limited by selection bias that could distort the estimate of the association between risk factors and disease. Additionally, among the *IDH1* non-p.R132 mutations, ie, G97D, S122N, G123E, I130K, and G131S, that we identified, only 2 had been reported previously. G97D-mutant *IDH1* had been found in colon cancer cell lines and G123E-mutant *IDH1* had been reported in acute myeloid leukemia (AML).[21,22] The clinical significance of these *IDH1* non-p.R132 mutations is also not certain. Not being able to draw a solid conclusion of significant prognostic difference between *IDH1* non-p.R132-mutant AAs and *IDH*-wildtype AAs could be related to a small number of such cases in this study.

Using the cBioPortal for Cancer Genomics (http://cbioportal.org) to analyze 794 gliomas from the Merged Cohort of LGG and GBM (TCGA, Cell 2016) showed that *BCAT1* amplification was noted in both wildtype (1.1%, 4/367) and *IDH*-mutant (2.3%, 10/427) gliomas. As *BCAT1* amplification might cause BCAT1 protein upregulation, using negative BCAT1 IHC as a surrogate marker to identify *IDH*-mutant gliomas could miss 2.3% of *IDH*-mutant cases. Further analysis of the *IDH*-mutant cases that co-occurred with *BCAT1* amplification showed that nine were *IDH1* R132H-mutant and one was *IDH1* R132S-mutant. Applying IDH1 H09 staining to identify these *IDH1* R132H-mutant tumors would greatly diminish the missing rate to 0.23% (1/427 cases).

The expression of *BCAT1* could also be affected by *MYC*. MYC transcription factor can increase *BCAT1* expression by binding to the promoter region of *BCAT1* in nasopharyngeal carcinoma,[23] and decreased *BCAT1* expression has been shown in *MYC*-knockdown hepatocellular carcinoma cells.[24] BCAT1 protein upregulation could be seen in gliomas with MYC protein upregulation. Indeed, in the cBioPortal datasets of the Brain Lower Grade Glioma (TCGA, Provisional) and the Glioblastoma Multiforme (TCGA, Provisional), MYC protein upregulation was noted in 6.4% (15/233) and 6.7% (1/15) of *IDH*-mutant gliomas, respectively. The sensitivity of BCAT loss for detecting *IDH* mutations could be lower in these tumors. However, using IDH1 H09 stain could improve this situation as 15 out of these 16 cases were *IDH1* R132H-mutant.

Using BCAT1 IHC for Screening of IDH Mutations

As BCAT1 loss is a consequence of *IDH* mutation and our study demonstrated that BCAT1 IHC staining had a high sensitivity to detect *IDH* mutations (96.7% and 100% for all *IDH* and canonical *IDH* mutations, respectively), we proposed that BCAT1 IHC could be used as a screening test for *IDH* mutations. Its high sensitivity (100%) for *IDH* mutations was also proved in our validation set. A flowchart for the work-up of gliomas was proposed in Figure 2. For tumors with low *IDH* mutation rates, such as anaplastic astrocytoma and glioblastoma, performing BCAT1 IHC prior to IDH1 H09 IHC might be more efficient. While for tumors with higher *IDH* mutation rates, such as diffuse astrocytoma and oligodendroglioma, performing IDH1 H09 IHC prior to BCAT1 IHC could be a better choice. DNA sequencing would only be needed in cases that were IHC negative for both BCAT1 and IDH1 H09. Of note, although *IDH1/2* mutations are not noted in PA and BCAT1 expression is expected, loss of BCAT1 was noted in 5 PAs in our study. The specificity of BCAT1 loss to detect *IDH1/2* mutations in PA (85.7%, 30/35) was similar to those in AA (86.4%, 51/59) and GBM (84.3%, 59/70). By using our advocated algorithm, only 23 AAs (BCAT1– and IDH1 H09–; 19.2%) rather than 76 AAs (IDH1 H09–; 63.3%) in the current study cohort would need DNA sequencing (Table S2 in **Supplemental Digital Content**). A more significant reduction from 70 cases (IDH1 H09–; 93.3%) to 11 cases (BCAT1– and IDH1 H09–; 15.7%) was noted in our validation study of primary GBMs (Table S4 in **Supplemental Digital Content**). Therefore, BCAT1 IHC should have tremendous implications in the evaluation of *IDH* mutation status.

Using BCAT1 IHC for the Classification of Diffuse Gliomas

ATRX is a marker mainly for distinguishing astrocytic and oligodendrogliotic differentiation of diffuse glioma.[4] Although ATRX loss is mostly restricted to IDH-mutant tumors,[15] the sensitivity of ATRX loss to identify *IDH* mutations was lower than that of BCAT1 loss. Diffuse gliomas with a positive BCAT1 staining would almost exclude the possibility of *IDH* mutations, and the need of 1p/19q assay could be decreased. As oligodendroglioma and anaplastic oligodendroglioma are IDH-mutant and 1p/19q-codeleted, 1p/19q assay is only required in IDH-mutant tumors.

Application of BCAT1 IHC in Other *IDH*-Mutant Tumors

Other than gliomas, *IDH* mutations have been reported in cartilaginous neoplasms (56%), AML (17%), cholangiocarcinoma (16%–36%), and prostate cancer (1.3%).[25-28] Different from gliomas that *IDH1* R132H mutation consisted of 85%–90% of the *IDH* mutations,[3,4] *IDH1* R132H mutation was much less common in cartilaginous neoplasms (17.3%), AML (15.5%), cholangiocarcinoma (17%), and prostate cancer (50%).[25,28-30] As BCAT1 IHC could detect *IDH1* non-R132H and *IDH2* mutations, it might have a role in the diagnostic work up of these tumors.

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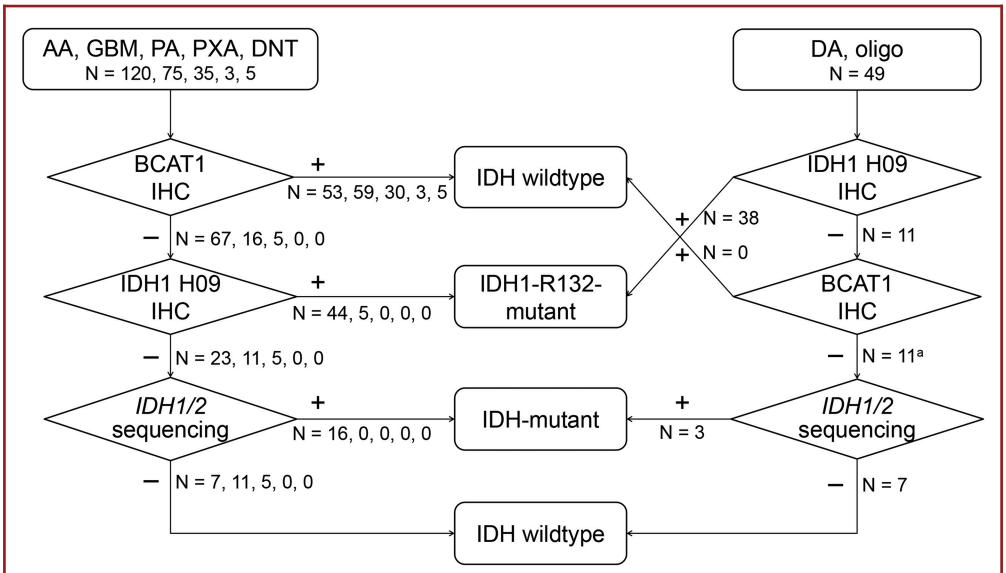


FIGURE 2. *Flowchart for testing of IDH status in gliomas. The numbers refer to the number of cases in the current study.* [a] *IDH1/2 sequencing was failed in one case. AA, anaplastic astrocytoma; DA, diffuse astrocytoma; DNT, dysembryoplastic neuroepithelial tumor; GBM, glioblastoma; oligo, oligodendroglioma; PA, pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma.*

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CONCLUSION

Our results showed that loss of BCAT1 IHC staining had a high sensitivity for *IDH* mutations. As all the cases with canonical *IDH* mutations in this study showed BCAT1 loss, a positive BCAT1 IHC staining might exclude canonical *IDH* mutations. Therefore, the IHC results of BCAT1 and IDH1 H09 could help in selecting cases for DNA sequencing of *IDH1/2* genes, and improve the cost-effectiveness of detecting *IDH1* non-R132H and *IDH2* mutations particularly in tumors with a low *IDH* mutation rate. Besides, the need of 1p/19q assay for oligodendrogliotic tumors could be decreased.

Disclosures

This work was supported by Taipei Veterans General Hospital (V105C-185, V105C-187, V106C-037) and Taiwan Ministry of Science and Technology (MOST 104-2320-B-075-003, MOST 104-2320-B-075-004). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Supporting Information. Table S1. Clinical features of 120 anaplastic astrocytomas by *IDH1/2* genotypes. **Table S2**. The associations between *IDH1/2* genotypes and immunostains for BCAT1 and IDH1 H09. **Table S3**. Clinical features of 120 anaplastic astrocytomas by the result of immunostains for BCAT1 and IDH1 H09. **Table S4**. Multivariate survival analyses of IDH1 H09 positivity, ATRX loss and BCAT1 loss. **Table S5**. BCAT1 and IDH1 H09 IHC staining results in 75 glioblastomas. **Table S6**. BCAT1 and IDH1 H09 IHC staining results in 49 grade II/grade III diffuse gliomas with oligodendroglioma-like morphology. **Table S7**. BCAT1 and IDH1 H09 IHC staining results in 35 pilocytic astrocytomas (PAs), 3 pleomorphic xanthoastrocytomas (PXAs) and 5 dysembryoplastic neuroepithelial tumors (DNTs). **Figure S1**. The flow diagram of study cohort. **Figure S2**. Two examples of discordant results between IHC and sequencing analysis. An *IDH* wildtype AA showing **A**, diffuse positive IDH1 H09 staining, and **B**, negative BCAT1 staining (loss of BCAT1 expression). An *IDH1* R132H-mutant AA showing **C**, negative IDH1 H09 staining, and **D**, negative BCAT1 staining of the tumor cells. The BCAT1 positive cells are microglia or histiocytes, which could be used as the internal positive control. Scale bars = 100 μm. **Figure S3**. Examples of equivocal BCAT1 IHC staining. **A**, An *IDH1* R132L-mutant AA and **B**, an *IDH1* R132H-mutant AA showing loss of BCAT1 staining in part of the tumor cells, while BCAT1 staining was positive in the others. **Figure S4**. Survival curves stratified by *IDH1/2* genotypes. **A**, Progression-free survival. **B**, Overall survival.

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Acknowledgments

The authors thank Chun-An Kuo, Shin-Ying Lin, Pao-Hua Huang, and Yung-Tsung Hong for their technical assistance.

COMMENTS

The addition of BCAT1 immunohistochemistry to the current diagnostic work up of brain tumors, which relies on immunohistochemistry for IDH1 R132H and ATRX protein expression, will enhance the identification of other less common mutated variants of IDH without any reliance on genotyping techniques. The authors have proposed diagnostic algorithm with incorporates the use of BCAT immunohistochemistry. Comprehensive identification of any brain tumors with any IDH mutation is essential in their proper prognostictation.

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IDH mutations are associated with better prognosis than IDH wild-type in astrocytic tumors. Although antibody specific to the IDH mutations has high sensitivity, in tumor types where IDH mutations are rare, confirmation of IDH mutation status in immune-negative tumors using sequencing will not be cost-effective. IDH mutations are associated with better prognosis than IDH wild-type in astrocytic tumors. Although antibody specific to the IDH mutations has high sensitivity, in tumor types where IDH mutations are rare, confirmation of IDH mutation status in immune-negative tumors using sequencing will not be cost-effective.

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Quality of Life Improvement Following Deep Brain Stimulation for Parkinson Disease: Development of a Prognostic Model

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Received, December 13, 2017.
Accepted, June 2, 2018.
Published Online, July 12, 2018.

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BACKGROUND: There is a growing attention to determine the factors that predict quality of life (QoL) improvement after deep brain stimulation (DBS) for Parkinson's disease. Prior literature has largely focused on examining predictors one at a time, sometimes controlling for covariates.

OBJECTIVE: To develop a model that could be used as a nomogram to predict improvement in QoL following DBS surgery in patients with Parkinson's disease.

METHODS: All patients with complete pre- and postoperative movement disorder and neuropsychological testing who underwent DBS at a single institution between 2007-2012 were analyzed. The Parkinson's Disease Questionnaire-39 (PDQ-39) was used to measure QoL. Potential predictive factors, including patient demographics, clinical presentation characteristics, radiographic imaging, and motor and psychological testing were analyzed for impact on QoL.

RESULTS: Sixty-seven patients were identified, 36 (53.73%) of whom had meaningfully improved QoL following surgery. Five baseline variables showed significant relationships with the outcome: years since symptom onset, percent change in *on/off* motor evaluation, levodopa equivalent daily dose, bilateral vs unilateral DBS implantation, and PDQ-39 score. The final model includes PDQ-39, percent change in UPRS-III, and years since symptom onset and is able to predict improvement in QoL with 81% accuracy.

CONCLUSION: Our model accurately predicted whether QoL would improve in patients undergoing subthalamic nucleus DBS 81% of the time. Our data may serve as the foundation to further refine a clinically relevant prognostic tool that would assist the decision-making process for clinicians and DBS multidisciplinary teams assessing patient candidacy for surgery.

KEY WORDS: Parkinson's disease, Statistical model, Deep brain stimulation, Subthalamic nucleus, Patient outcome assessment

Neurosurgery 85:343–349, 2019 DOI:10.1093/neuros/nyy287 www.neurosurgery-online.com

Deep brain stimulation (DBS) is an established therapy for Parkinson's disease (PD). Since its introduction in the 1990s,[1] several randomized controlled studies have corroborated the benefits of high frequency stimulation for PD, compared the results from the different targets, and reported the complication rate.[2-5] Furthermore, attempts have been made to improve the technique and to identify methods for lead implantation in order to obtain optimal results.[6-10] However, decision-making at the level of an individual patient is still challenging even for experienced movement disorder groups.[11]

Rigorous patient selection criteria are essential to surgical outcomes. Previous work has largely focused on evaluating predictors of surgical outcomes by testing hypotheses of association or estimating the magnitude of effects.[12-16] Alternatively, prognostic modeling seeks to maximize the discriminatory ability of a model: a strong

ABBREVIATIONS: BDI, Beck Depression Inventory; **CI,** confidence interval; **DBS,** deep brain stimulation; **LEDD,** levodopa-equivalent daily dose; **OR,** odds ratio; **PD,** Parkinson's disease; **PDQ-39,** Parkinson's Disease Questionnaire-39; **QoL,** quality of life; **ROC,** Receiver operating characteristic; **SD,** standard deviation; **STN,** subthalamic nucleus

association detected when a group is analyzed does not always coincide with robust discriminatory ability at the individual level. Multiple clinical factors, when considered together, may improve the selection of surgical candidates.

The patient's quality of life (QoL) after surgery is perhaps the best surrogate marker of success. There is growing interest in finding the preoperative factors that could best predict QoL improvements after DBS surgery.[13,17] Our aim in this study is to start developing a model to predict improvement in QoL following subthalamic nucleus (STN) DBS for PD. We used preoperative patient characteristics and imaging data that would be available in most movement disorders practices regularly performing DBS.

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METHODS

With Institutional Review Board approval, we retrospectively identified all patients with complete pre- and postoperative movement disorder evaluations who underwent STN DBS surgery between 2007 and 2012. This study was exempted from obtaining individual informed consent given its retrospective nature and minimal risk. Out of 230 patients who underwent surgery during this period, 67 were included in our study. The Parkinson's Disease Questionnaire-39 (PDQ-39) assessment is part of the Neuropsychology Registry at our center. Exclusions were primarily due to nonreferral, lack of postoperative evaluation, and refusal of testing. The mean age of the nonincluded patients was 63.84 (standard deviation [SD] =9.63) and 70.6 % were male which is similar to our included. The number of unilateral implants was 59.8% among the nonincluded patients which is also similar to the proportion among the included patients.

We gradually changed from UPDRS III to MDS-UPDRS III score by the end of this period. Therefore, for the sake of consistency, we included only patients with UPDRS III score. Surgical method and techniques in our institution are published elsewhere.[18] All patients from this cohort underwent levodopa challenge testing and a complete neuropsychological evaluation that included analysis of multiple cognitive domains as well as the Beck Depression Inventory- 2nd edition (BDI-II).[13]

Outcomes

The PDQ-39, the most widely used disease-specific measure of health-related-QoL,[19] was used to measure QoL. The PDQ-39 generates summary index scores (PDSI) on a scale of 0 to 100, with higher scores indicating worse QoL.[19] The PDQ-39 was administered as standard of care preoperatively within 6 mo prior to surgery and again between 6 and 12 mo following surgery. A preoperative to postoperative decrease of 10.9 PDSI units or greater was used to indicate the presence of clinically relevant improvement in QoL. This cutoff is based on previous work that demonstrated 10.9 units as a threshold indicative of a significant change in QoL.[17]

Predictive Factors

Preoperative patient characteristics and assessments that are frequently available before surgery were analyzed. Preoperative candidate predictors considered for the model included: age at surgery; sex; preoperative percent change in *on/off* UPDRS-III total score; years since symptom onset (disease duration); age of first symptom onset; laterality of first symptoms (right, left, bilateral); laterality of surgery (right vs left and unilateral vs bilateral); levodopa-equivalent daily dose (LEDD); presence or absence of dopamine agonist use; Beck Depression Inventory-2nd Edition (BDI-II); PDQ-39 summary index score. Furthermore, third ventricle width and bicaudate ratio were also examined as indirect measures of total brain atrophy.[20,21]

Statistical Methods

Descriptive statistics were calculated for the full sample and the sample stratified by outcome group. Unadjusted odds ratios (ORs) were computed separately for each candidate predictor using simple logistic regression.

Best subsets selection[22] was used to determine which predictors would be included in the final logistic regression model. This technique uses a branch-and-bound algorithm to generate best models for each possible number of predictor variables using the global chi-square statistic, with the goal of selecting a subset of variables with the best discriminatory ability, regardless of magnitude or significance of association. The discriminatory ability of the final model was assessed using the c-statistic (equivalent to the area under the receiver operating characteristic (ROC) curve). The c-statistic ranges from 0.5 to 1.0, with a value of 0.5 indicating that the model performs no better than a coin toss, and a value of 1.0 indicating that the model will correctly classify 100% of patients. In brief, it is calculated by taking all possible pairwise comparisons from the sample, wherein 1 patient achieved improvement and one did not. The c-statistic represents the percentage of time that the model assigned a higher probability of improvement to the patient who actually achieved improvement. An ROC curve was plotted to allow clinicians to select appropriate probability thresholds to achieve their preferred balance of sensitivity and specificity. The ROC curve for the model is presented in Figure 2.

Bootstrap resampling was used to validate the model.[23] By resampling the original dataset with replacement, 500 alternate datasets of the same size of the original were generated. The final model was applied to each alternate dataset and Harrell's optimism was calculated to adjust the c-statistic accordingly.[24] Goodness-of-fit was assessed using the Le Cessie & Houwelingen test.[25] A prognostic nomogram was created for clinical utility (Figure 3).

A sensitivity analysis was performed with alternate thresholds for PDSI change to determine how the model would perform with both more and less strict criteria for designating clinically meaningful improvement in PDQ-39.

Analyses were conducted on complete cases using SAS Studio v. 3.5 (SAS Institute, Cary, North Carolina) and R v. 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Sixty-seven patients who underwent STN-DBS for PD at our institution between 2007-2012 were identified with pre- and postoperative PDQ-39 scores, 36 (53.73%) of whom had improved QoL following surgery (of those classified as "not improved," only 3 patients declined; the remainder were stable). The sample was predominantly male (73.13%) and white (98.51%) with an average age of 62.79 yr (SD = 7.68) and disease duration of eleven years (SD = 5.44). The median percent of change in preoperative *on/off* UPDRS III score was 44%

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TABLE 1. Preoperative Sample Characteristics and Summary of Results

Patient characteristics	Full sample n = 67	Improved n = 36	Did not improve n = 31
Male, n (%)	49 (73.13)	24 (66.67)	25 (80.65)
White, n (%)	66 (98.51)	36 (100)	30 (96.77)
Age at surgery, mean (SD)	62.79 (7.68)	62.64 (6.91)	62.97 (8.6)
Disease duration, mean (SD)	11.07 (5.44)	12.33 (4.79)	9.61 (5.85)
Age of symptom onset, mean (SD)	50.78 (8.82)	49.36 (8.17)	52.42 (9.39)
Laterality of first symptoms*, n (%)			
Right	39 (59.09)	22 (62.86)	17 (54.84)
Left	24 (36.36)	11 (31.43)	13 (41.94)
Bilateral	3 (4.55)	2 (5.71)	1 (3.23)
Laterality of surgery, n (%)			
Right	13 (19.4)	4 (11.11)	9 (29.03)
Left	32 (47.76)	16 (44.44)	16 (51.61)
Bilateral (including staged procedures)	22 (32.84)	16 (44.44)	6 (19.35)
Dopamine agonist use, n (%)	39 (58.21)	20 (55.56)	19 (61.29)
Preoperative UPDRS-III *off* meds Mean(SD)	41.14 (12.78)	40.42 (12.32)	41.82 (13.35)
Preoperative UPDRS-III *on* meds Mean (SD)	21.57 (9.33)	20.99 (9.1)	22.29 (9.72)
Percent change in *on/off UPDRS*-III, Median (IQR)	44 (30)	54 (22)	36 (24)
LEDD, mean (SD)	1057.9 (530.4)	1188.3 (579.2)	906.4 (428.3)
BDI-II, mean (SD)	11.06 (6.99)	11.92 (7.17)	10.06 (6.76)
Bicaudate Index mean, (SD)	0.124 (0.024)	0.122 (0.026)	0.126 (0.022)
Third ventricle width Median (IQR)	4 (3)	4 (2.5)	5 (3)
QoL (PDQ-39), median (IQR)	28.33 (22)	36.38 (18.54)	20.63 (25)

*data missing at 1.5%, LEDD: Levodopa equivalent daily dosage.

(IQR = 30). Data were nearly complete; 1 patient had missing data on one variable (laterality of first symptoms). Further sample characteristics such as disease duration, age of symptom onset, laterality of first symptoms, laterality of the implant, dopamine agonist use or not at the time of preoperative interview, LEDD, BDI-II, bicaudate index and third ventricle width, as well as a summary of outcomes for each characteristic can be found in Table 1.

Table 2 includes unadjusted ORs for bivariable analyses assessing the magnitude of association between each candidate predictor and the outcome. Five variables showed significant relationships with the outcome. For every additional year since symptom onset, patients displayed an 11% higher odds of improvement in QoL (OR = 1.11, 95% confidence interval [CI] 1.001-1.231, $P = .048$). Patients who underwent bilateral DBS implantation had 6 times the odds of improvement in QoL when compared to those who underwent right-sided DBS (OR = 6.0, 95% CI 1.331-27.047, $P = .02$). For every additional 1% on versus *off* medication change in UPDRS-III total score, the odds of improvement increased 4.5% (OR = 1.045, 95% CI 1.014-1.078, $P = .005$). Odds of improvement increased 12.4% for every additional 100 units LEDD a patient was prescribed preoperatively (OR = 1.124, 95% CI 1.008-1.254, $P = .036$). Every one point increase in preoperative PDQ-39 score (indicating worse QoL) yielded a corresponding 7.3% increase in odds of improvement (OR = 1.073, 95% CI 1.03–1.119, $P = .001$).

TABLE 2. Unadjusted Association Between Each Predictor and Improvement in QoL

	Unadjusted odds ratio (95% CI)	*P*-value
Male	0.48 (0.155-1.484)	.203
Age at surgery	0.994 (0.934-1.059)	.86
Disease duration	1.11 (1.001-1.231)	.048
Age of symptom onset	0.959 (0.905-1.017)	.161
Laterality of first symptoms*		
Right	reference	ref
Left	0.654 (0.235-1.818)	.415
Bilateral	1.545 (0.129-18.498)	.731
Laterality of surgery		
Right	reference	ref
Left	2.25 (0.574-8.824)	.245
Bilateral (including staged procedures)	6.0 (1.331-27.047)	.02
percent change in *on/off* UPDRS-III	1.045 (1.014-1.078)	.005
LEDD (*100)	1.124 (1.008-1.254)	.036
Dopamine agonist use	0.789 (0.297-2.097)	.635
BDI - II	1.04 (0.968-1.118)	.281
Bicaudate Index (*100)	0.932 (0.759-1.144)	.5
Third ventricle width	0.928 (0.734-1.173)	.533
QoL (PDQ-39)	1.073 (1.03-1.119)	.001

*data missing on one patient.

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TABLE 3. Model Coefficients and Adjusted Odds Ratios

	Coefficient	OR (95% Confidence interval)	*P*-value
Intercept	− 5.221		
PDQ-39	.067	1.069 (1.021-1.119)	.005
percent change in *on/off* UPDRS-III	.049	1.051 (1.013-1.09)	.009
Years since symptom onset	.114	1.121 (.992-1.267)	.067

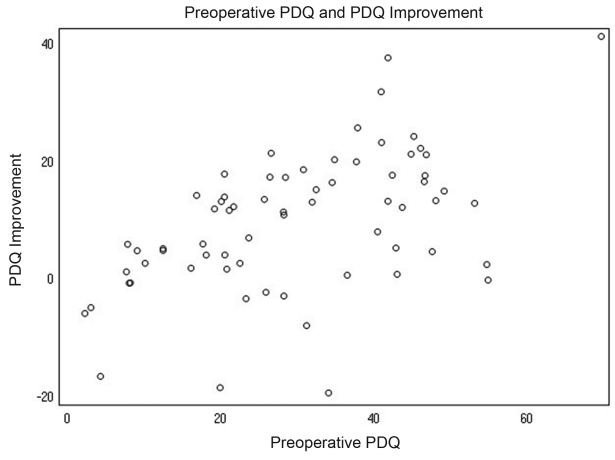


FIGURE 1. *Scatterplot showing the correlation between preoperative PDQ-39 and the raw improvement after surgery.*

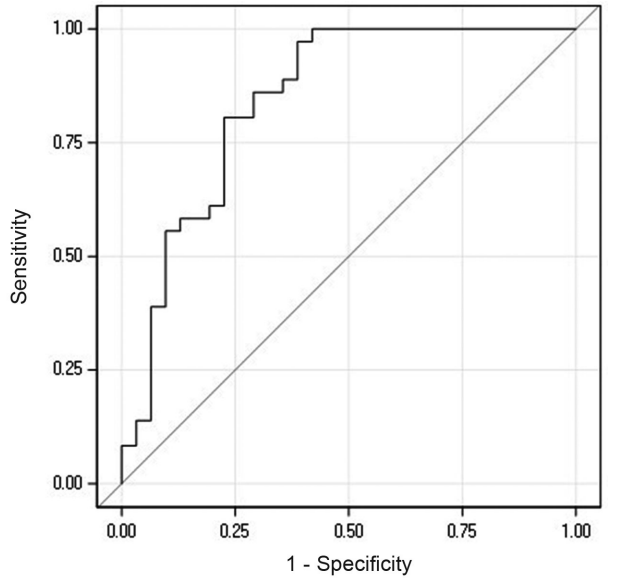


FIGURE 2. *Receiver operating characteristic (ROC) curve for the model.*

Following the 10 events per variable rule,[26] 3 variables were included in the final model: PDQ-39, percent change in UPRS-III, and years since symptom onset. Model coefficients and ORs can be found in Table 3. While controlling for covariates, odds of improvement calculated by comparing preoperative to postoperative PDQ-39 increased 6.9% for every point increase in PDQ-39 and 5.1% for every additional 1% change in UPDRS-III. A scatterplot showing the correlation among preoperative PDQ-39 and the raw improvement after surgery is displayed in Figure 1. Years since symptom onset served to increase the predictive ability of the model. Model discrimination was very good, with the inclusion of these 3 variables, with an optimism-adjusted c-statistic of 0.814 (unadjusted c-statistic = 0.843). Given 2 future patients, 1 from each outcome group, there is an 81.4% chance that this model would correctly predict which of the 2 would improve in QoL following surgery. Model fit was acceptable according to the Le Cessie & Houwelingen test. The ROC curve for the model is presented in Figure 2. The prognostic nomogram is presented in Figure 3.

The sensitivity analysis indicated that our model would perform well when applied to other thresholds to designate improvement, though discrimination is best when utilizing the threshold selected for the current study (Table 4).

DISCUSSION

In this study, we assembled a model that predicted improvement in QoL with 81% accuracy in PD patients who underwent STN–DBS surgery. While the availability and amount of information that health care professionals receive is increasing exponentially, this extensive and growing body of literature is constantly challenging our decision-making process due to varying recommendations.[11,27] When considering outcomes following DBS among PD patients, prior literature has largely focused on examining predictors one at a time, sometimes while controlling for covariates. The analysis tends simply to quantify the magnitude of an effect. In contrast, multivariable prediction models seek to combine several clinical correlates with the goal of predicting the outcome with the highest accuracy possible. Previously, Okun et al[9] developed a comprehensive 5-section questionnaire, with the purpose of identifying ideal surgical candidate among parkinsonian patients based on patient's scores. Our model, in contrast, is not intended to be a screening tool to determine surgical candidacy. Instead, when a

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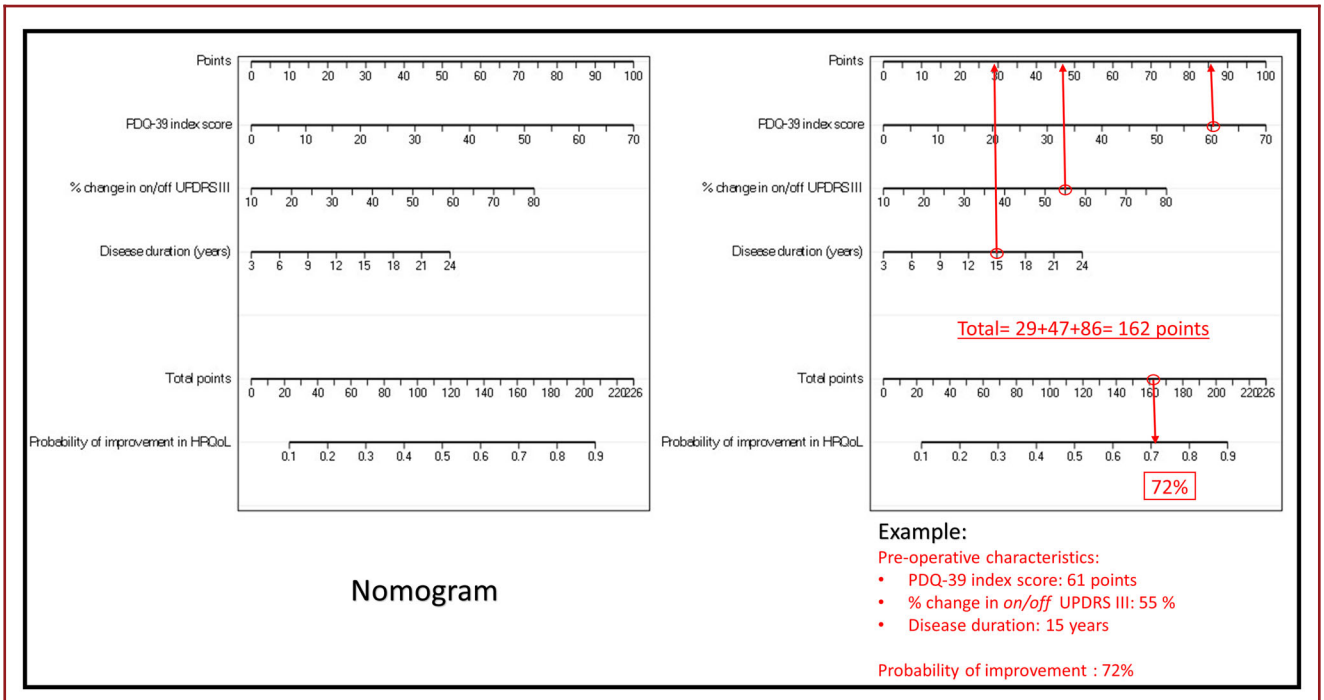


FIGURE 3. *To use the nomogram, locate the patient's position on the scale associated with each predictor. The top axis displays prognostic points. Connect the position on each variable axis with the "Points" (top) axis to determine the number of points corresponding to the appropriate variable position. Total the points for all variables, then find the appropriate position on the "Total points" axis and connect it with the associated position on the "Probability of improvement in QoL" (bottom) axis to approximate the patient's probability of improvement. See the example explained in the right figure.*

TABLE 4. Model Performance Applied to Alternative PSDI Thresholds

Cutoff for improvement	Number classified as improved	Unadjusted c-statistic	Goodness-of-fit test*
0	53	.8	.717
5	43	.776	.09
10.9	31	.843	.612
15	22	.815	.229
20	12	.829	.599

*P-value < .05 indicates unacceptable fit.

multidisciplinary approach is used to select surgical candidates, our model can contribute to the decision-making process by identifying which patients could expect significant gains in QoL.

Using PDQ-39 as outcome measure, our model included 3 predictors: preoperative PDQ score, preoperative percent change in *on/off* UPDRS-III and disease duration. Worse preoperative PDQ scores and better response to levodopa predicted higher odds of improvement in QoL. In our sample, a worse preoperative QoL predicted improvement. To some degree, such a relationship is expected with longitudinal data; those with exceptionally high baseline scores can only be expected to either improve or remain stable over time. However, our use of a previously published reliable change index mitigates much of the effect observed by expected regression to the mean.

Preoperative motor response to levodopa was associated with the QoL outcome in our study. Levodopa response is also widely accepted as the best predictor for motor outcome after DBS.[5,14,15,28-30] Previously, our group identified several independent nonmotor predictors for PDQ-39 score outcome, including preoperative PDQ-39, BDI score and single-trial learning on the Rey's Auditory Verbal Learning Tests.[31] Other groups have demonstrated that cumulative daily *off* time at baseline as the most important predictor of better QoL outcome following DBS surgery.[17] Although the absence of an improvement in QoL may not be explained solely by the motor outcomes,[13] QoL improvement has been associated with preoperative response to levodopa[12] and motor outcome.[17,32] Furthermore, when used in combination with other predictors, as in our model, levodopa response may play an important role to predict postoperative QoL outcomes. Cumulative daily *off*-time was not added as a possible predictor in our study since we did not have these data in our records but certainly seems to be a promising predictor to be tested in future prospective models.

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Previous meta-analysis reporting the improvement in QoL using PDQ-39 described an average improvement of 34.5% (SD = 15.3%)[5] and also a range from 14% to 62%.[33] More recently, in another meta-analysis of randomized controlled trials from 2014 the weighted mean difference in PDQ-39 was 7.43 points.[34] Few works have focused on QoL improvement after unilateral STN-DBS. Slowinski et al[35] showed that unilateral stimulation may provide improvement in total health-related quality-of-life measures of approximately 15% on the total score of QoL. Among the patients in the COMPARE trial, the mean improvement was 15% among the ones treated with STN–DBS.[36] The median improvement in QoL in our cohort was 38.1% (9.9 points) among all patients, 44.1% (13.9 points) among patients undergoing bilateral procedures and 34.6% (7.9) points among the patients treated with unilateral procedures. Although in bivariate analyses, bilaterally treated patients were more likely to improve following surgery, bilateral versus unilateral implantation did not provide enough discriminatory ability to warrant inclusion in the final model. It is worth mentioning that, among the 45 patients who initially had a unilateral implant, nine patients underwent subsequent contralateral lead implantation within 2 yr after the postoperative evaluation. The accuracy of this model among patients with initially asymmetric disease needs to be better investigated in the future.

Traditional multivariable model-building techniques often exclude independent variables that are not significantly associated with the outcome. In our final model, disease duration, which does not display a significant association when controlling for the other two variables that were included. However, when added to the model, it improves the model's ability to accurately predict the outcome. Failing to include, it would result in an unadjusted c-statistic of 0.814 or a model with 3% lower discriminatory ability. Health-related QoL measures are inherently affected by characteristics of the individual and the environment and may be confounded by prior disease status.[37] Thus, patients with longer disease duration may perceive their QoL improvement differently when compared with patients with earlier onset of the disease.

Neither of the imaging variables we included in this model were associated with outcome. This may be related to the lack of sensitivity and specificity as they relate to one slice and not a global measure.[38] Recently, automated measures of cortical thickness and measures of preoperative brain metabolism have emerged as predictors of outcome when DBS is used for PD.[39,40]

Limitations

The use of prediction models does not supersede the judgment of experienced healthcare professionals and should not be used as a replacement. Understanding subtle differences among populations together with a patient's goals still confound standard clinical research methods.[41] Although our model shows promise in predicting QoL following DBS, it does have limitations. Our sample size is limited and some patients did not return for postoperative neuropsychological testing. For these patients, we did not have PDQ-39 outcome. This model could be improved with a larger sample and the addition of other variables. Additionally, it could be strengthened by applying it to an external data set, validating it using MDS-UPDRS III scale and eventually testing it prospectively before clinical application. Moreover, while the optimism-adjusted c-statistic of 0.81 in our sample is considered excellent discrimination for a prediction model, this model would benefit from external validation separately in several areas: bilaterally and unilaterally implanted patient populations; different stages of the disease, with early motor complications; and using a longer follow-up. This would allow us to best determine whether the model may perform differently in each population and at different follow-up time. For instance, among patients with early motor complications, less improvement in QoL may be advantageous compared to a cohort under medical therapy alone since the QoL among patients under medical therapy alone frequently tends to worsen.[42] Nevertheless, we are optimistic that this tool can be refined and offer real-world clinical utility.

CONCLUSION

Our model could accurately predict whether postoperative QoL will improve 81.4% of the time. Our data thus far indicate that it may be possible to build a more comprehensive prediction model that could serve as a clinically relevant prognostic tool for clinicians assessing patient candidacy for surgery.

Disclosures

Dr Machado receives consulting fees from St. Jude and has distribution rights from Enspire, ATI, and Cardionomics. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Optimizing Outcome Prediction Scores in Patients Undergoing Endovascular Thrombectomy for Large Vessel Occlusions Using Collateral Grade on Computed Tomography Angiography

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on behalf of collateral-based resetting of endovascular treatment for acute stroke; CoSETS investigators

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Received, March 7, 2018.
Accepted, June 17, 2018.
Published Online, July 13, 2018.

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BACKGROUND: Although several outcome prediction scores incorporated with pretreatment variables have been developed for acute ischemic stroke (AIS) patients, there is not currently a prediction score that includes pretreatment imaging that can show salvageable brain tissue.

OBJECTIVE: To evaluate whether addition of the collateral grade on computed tomography angiography to previously published prediction scores could increase accuracy of clinical outcome prediction in endovascular thrombectomy (EVT) for AIS.

METHODS: This study used a retrospective multicenter registry for patients undergoing EVT for anterior circulation large vessel occlusion. Three previously published outcome prediction scores (Houston intra-arterial therapy 2, HIAT2; totaled health risks in vascular events, THRIVE; and Pittsburgh response to endovascular therapy, PRE scores) were tested in this study. Using 482 deprivation cohorts, areas under the receiver operating characteristic curves (AUC-ROCs) were compared between prediction scores with/without collateral grades in predicting the poor outcomes (modified Rankin Scale 4-6 at 3-mo follow-up) after EVT. We developed modified prediction scores by adding the collateral grade, and their advancement of outcome prediction was validated using 208 independent validation cohorts.

RESULTS: AUC-ROCs of HIAT2, THRIVE, and PRE scores that incorporated with collateral grade were superior in predicting poor outcomes when compared to that of the unmodified scores ($P < 0.001$). In modified prediction models, 3, 3, and 10 points were added for poor collateral grade to HIAT2, THRIVE, and PRE score. Modified models outperformed unmodified models in testing of the validation cohorts ($P < 0.001$).

CONCLUSION: The addition of the collateral grade to outcome prediction scores resulted in better prediction of poor outcome after EVT for AIS compared to the prediction scores alone.

KEY WORDS: Ischemic stroke, Outcome prediction scores, Mechanical thrombectomy, Collateral circulation

Neurosurgery 85:350–358, 2019 DOI:10.1093/neuros/nyy316 www.neurosurgery-online.com

ABBREVIATIONS: AF, atrial fibrillation; **AIS,** acute ischemic stroke; **ASPECTS,** Alberta Stroke Programme Early CT score; **AUC-ROCs,** areas under the receiver operating characteristic curves; **CT,** computed tomography; **CTA,** computed tomography angiography; **DM,** diabetes mellitus; **EVT,** endovascular thrombectomy; **HIAT2,** Houston intra-arterial therapy 2; **HTN,** hypertension; **IDI,** integrated discrimination improvement; **LVO,** large vessel occlusion; **mHIAT2,** Modified HIAT2; **mPRE,** modified PRE; **mRS,** modified Rankin Scale; **mTHRIVE,** modified THRIVE; **mTICI,** modified thrombolysis in cerebral ischemia; **NIHSS,** National Institute of Health Stroke Scale; **NRI,** net reclassification improvement; **PRE,** Pittsburgh response to endovascular therapy; **SVM,** support vector machine; **THRIVE,** totaled health risks in vascular events

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Due to the consistent results of international, randomized controlled trial studies, endovascular thrombectomy (EVT) is now accepted as standard management for acute ischemic stroke (AIS) related to large vessel occlusion (LVO).[1] Because the selection criteria for EVT, composed of the time window from symptom onset to treatment and the size of infarct core, is broad, a considerable proportion of AIS patients did not have the benefit of EVT despite successful recanalization, or some patients lose the opportunity to benefit from treatment.

Enhancement of the efficacy of EVT for AIS patients has important clinical implications, and, therefore, it may be rather important to design a patient-selection algorithm for predicting long-term outcomes after EVT. Early identification of patients with a very high likelihood of poor outcome after EVT may promote cost-effective patient triage and healthcare resource allocation. Thus, researchers have attempted to derive patient-selection algorithms by combining known clinical risk factors that are available quickly after patient admission.

Several previous studies have identified a number of factors that independently contribute to long-term outcomes after EVT for AIS using the baseline information or laboratory values obtained from patients at admission. These factors comprised severity of symptoms, age, blood glucose level, cardiovascular risk factors, interval of ictus, time from symptom onset to treatment, and Alberta Stroke Programme Early CT score (ASPECTS) on baseline brain computed tomography (CT).[2-6] Collateral circulation has also been widely accepted as an independent factor contributing to predicting outcomes after reperfusion therapy for AIS.[7-9] Using computed tomography angiography (CTA), collateral circulation status in the ischemic hemisphere can be reliably measured by comparing backfilling pial arteries beyond the culprit artery to the opposite unaffected hemisphere, predicting salvageable brain tissue without additional computer-added processing. We hypothesized that previous prediction models could be improved to better stratify patients for EVT by inclusion of collateral status on brain CTA. However, although collateral grade is early and simple information that can be derived from AIS patients, global risk prediction models incorporating collateral grade on CTA have not yet been developed for clinical use.

In this study, we combined predictive scoring models and collateral grade on CTA to optimize scores that would better predict outcomes after EVT for AIS. Then, we validated whether the modified scoring models incorporating collateral grade were more beneficial than conventional scoring models for predicting poor outcome using an independent dataset.

METHODS

Subjects

We obtained demographic and clinical data, radiological data, and 3-mo functional outcomes using the modified Rankin Scale (mRS) from the collateral-based resetting of endovascular thrombectomy for acute stroke retrospective (CoSETS-retrospective) registry. The CoSETS-retrospective registry is a retrospective record of the prospectively registered cohorts who underwent EVT for AIS with anterior circulation LVO (**Supplemental Digital Content 1**, detailed description of study design), and a total of 16 comprehensive stroke centers participated in this registry between September 2010 and December 2015. Study enrollment criteria were as follows: (1) age ≥18 yr; (2) initial National Institute of Health Stroke Scale (NIHSS) ≥ 4; (3) onset-to-puncture time was equal to or less than 600 min; (4) mRS before qualifying stroke was 0 or 1; (5) collateral grading assessable on CTA; and (6) recanalization success assessable on catheter angiogram during the procedure. The Institutional Review Boards of all participating hospitals approved this study and waived the requirement for written informed consent for study inclusion based on the retrospective study design.

Imaging Analysis

Two neuroradiologists independently assessed the images for ASPECTS and collateral status on CTA using a commercialized DICOM viewer (OsiriX, Pixmeo, Geneva, Switzerland). ASPECTS was evaluated on images of 5-mm-thickness CT. CTA collateral grade was assessed on 20-mm-thickness, maximum intensity projection images from single-phase CTA or the first phase of multiphase CTA if multiphase CTA was obtained. CTA collateral grade was dichotomized into either good or poor. Poor collateral was defined as few or no vessel markings in more than half of the MCA territory on the affected side, as previously published.[10] Kappa values for inter-rater agreement of ASPECTS (≤7 vs 8-10) and CTA collateral grade (good vs poor) were 0.657 and 0.875, respectively. Discrepant cases were resolved by consensus between raters who remained blind to both the patient's clinical outcome and findings on follow-up CT or magnetic resonance imaging. To reduce misclassification of patients to the good or poor collateral groups, we excluded patients with poor CTA image quality, or patients in whom vessel markings were not well visualized in the contralateral hemisphere upon analysis.

Measurements of Conventional Prediction Score

We identified prediction-scoring models that were proven these simplicity and predictability of clinical outcomes in EVT through a literature review, and enrolled 3 prediction scores; Houston intra-arterial therapy 2 (HIAT2) score, the totaled health risks in vascular events (THRIVE) score, and the Pittsburgh response to endovascular therapy (PRE) score.[2,4,11] To calculate these scores, we noted the age, initial NIHSS, the presence or absence of hypertension (HTN), diabetes mellitus (DM), or atrial fibrillation (AF), initial glucose level, and ASPECTS of each patient.

We calculated 3 outcome prediction scores (HIAT2, THRIVE, PRE score) to serve as independent predictors of clinical outcomes. HIAT2 scoring system assigns 2 points for age of 60 to 79 yr, 4 points for age of 80 yr, 1 point for NIHSS of 11 to 20, 2 points for NIHSS score of ≥21, 1 point for a glucose level of ≥150 mg/dL, and 3 points for ASPECTS. The THRIVE scoring system assigns 1 point for an age of 60 to 79 yr, 2 points for an age of 80 yr, 2 points for an NIHSS score of 11 to 20, 4 points for an NIHSS score ≥21, and 1 point each for the presence of HTN, DM, or AF. The PRE score was calculated as age (years) +2 × NIHSS-10 × ASPECTS (Table 1).

Outcomes were dichotomously classified as poor (mRS 4-6 at 3-month follow-up) or good. Successful recanalization was defined as a modified thrombolysis in cerebral ischemia (mTICI) score of 2b or 3 at

TABLE 1. Scoring Method of HIAT2, THRIVE, and PRE Scores

HIAT2 score	Points	THRIVE score	Points
Age, yr		Age, yr	
≤59	0	≤59	0
60 to 79	2	60 to 79	1
≥80	4	≥80	2
NIHSS score		NIHSS score	
≤10	0	≤10	0
11 to 20	1	11 to 20	2
≥21	2	≥21	4
Glucose, mg/dL		Medical history	
<150	0	Diabetes mellitus	1
≥150	1	Atrial fibrillation	1
ASPECTS		Hypertension	1
8 to 10	0		
≤7	3		
Range of possible scores	0 to 10	Range of possible scores	0 to 9
Modification			
Collateral grade		Collateral grade	
Good	0	Good	0
Poor	3	Poor	3
Range of possible scores	0 to 13	Range of possible scores	0 to 12

PRE score = age (yr) + 2 × NIHSS-10 × ASPECTS + (modification: 10 points for poor collateral).

the completion of the EVT procedure.[12] Of the 690 patients identified, we randomly selected 70% (482) of these patients for the derivation cohort; the remaining 30% (208) were used for our validation cohort. Basic information was compared between the two groups using chi-squared tests and unpaired *t*-tests.

Statistical Analysis

Statistical analysis was conducted in 2 stages: the first analysis was to assess whether the addition of the CTA collateral grade to the 3 conventional prediction scores improved poor outcome prediction after EVT for AIS using the deprivation dataset. Under perspectives driven from the first analysis, second analysis was done to make a modified equation of the 3 prediction scores weighted with the poor collateral score, and to validate this modified equation using the validation dataset.

First, a logistic regression model was fitted to the data to determine the influence of predictive scores alone and scores adjusted using the collateral grade. The log odds for each subject were used to compare area under the receiver operating characteristic curve (AUC-ROC) between three prediction scores with/without the collateral grade.

Change of predictability in accordance with collateral grade was graphically represented using a predictiveness curve.[13] This curve is a graphical display of the distribution of risk defined by the following conditional probability: risk (y) = P[D = 1|Y = y], where D denotes the binary outcome (in our case, poor outcome) and Y = y is a marker value (in our case, a predictive curve with/without collateral grade). The interpretation of this curve is straightforward: a marker that is useless assigns equal risk to all individuals, and hence, the corresponding predictiveness curve is a horizontal line at the prevalence of the poor outcome; however, a marker that is highly informative of risk yields a predictive curve that is close to a step function.

To explore the influence of recanalization time and recanalization status on the prediction model with/without collateral grade, the subjects were divided into onset-to-puncture time groups (within 3 h, 3-6 h, and over 6 h) and recanalization status after EVT (mTICI grade 1-2a and 2b-3). We calculated the AUC-ROC, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) in each of these groups.[14]

Second, we designed modified prediction scores by adding the collateral grade using a linear kernel-based support vector machine (linear SVM). The following formula was used: $z = x + a \times y$, where z denotes the predictive value for poor outcomes, x is the given predictive score (HIAT2, THRIVE, or PRE score), y is the collateral grade, and a is a constant integer, to decide the most predictable equation. The training dataset was composed of 70% of patients randomly selected from the derivation cohorts, while the remaining 30% of patients from the derivation cohorts were used as a test dataset. Linear SVM processing was performed using MATLAB (MathWorks, Natick, Massachusetts).

The ability of the modified equations of the three prediction scores to predict poor outcomes was validated using the validation dataset. The AUC-ROC of the conventional and modified prediction scores for discriminating poor outcome was compared. Each modified and conventional predictive score was trichotomized into low-, intermediate-, and high-risk points, and the rate of poor outcome for each 3 risk point was graphically represented using bar-graphs.

RESULTS

Comparison Between Deprivation and Validation Datasets

The patient's age, sex, NIHSS, comorbidities, and CT findings (ASPECTS and collateral grade on CTA), rate of poor outcome, onset-to-puncture time, and recanalization status are shown in Table 2. These variables were not significantly different between the deprivation and validation datasets.

Value of Adding the Collateral Grade to 3 Conventional Prediction Scores

Due to missing data from certain subjects, 23 and 2 patients could not be scored with HIAT2 and PRE scores, respectively. The AUC-ROC of each predictive score with the addition of collateral grade was superior to that of the predictive score alone (HIAT2 score with/without collateral grade, 0.677 vs 0.768; THRIVE score with/without collateral grade, 0.685 vs 0.771; and PRE score with/without collateral grade 0.716 vs 0.784, $P < .001$; Figure 1).

Analysis of the predictiveness curves with/without the collateral grade revealed that collateral grade contributed to a better performance of the clinical models. The slope of the three models with the collateral grade was steeper (39.4%) from high risk over current prevalence of poor outcome compared to the models without the collateral grade (Figure 1).

Comparison of the AUC-ROC and continuous NRI and IDI revealed the benefit of adding the collateral grade to the prediction models for predicting poor outcomes in all three time-window groups. However, addition of collateral grade did not affect the

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TABLE 2. Comparison Between Derivation and Validation Cohorts

Variables	Derivation cohort (482)	Validation cohort (208)	*P*-value
Age	67.65 (SD:11.84)	67.76 (SD:13.60)	.542
Sex (female)	55.3%	54.3%	.808
Hypertension	60.2%	62.5%	.564
Diabetes	26.6%	24.5%	.575
Atrial fibrillation	52.1%	50.5%	.701
High glucose (≥150 mg/dL)	29.9%	24.5%	.159
Poor collateral grade	16.6%	16.8%	.941
Poor mRS (4-6) on 3mo	38.0%	40.4%	.55
Symptom onset to puncture time	233.6 (SD:114.58) min	234.3 (SD: 97.13) min	.529
Recanalization (mTICI 2b-3)	80.9%	78.8%	.531
ASPECTS	Median 8 (IQR:7-9)	Median 8 (IQR:7-9)	.107
NIHSS	Median 15 (IQR:11-19)	Median 15 (IQR:11-19)	.882

ASPECTS, Alberta Stroke Program Early CT Score; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Ischemia; NIHSS, National Institute Health Stroke Scale; SD, standard deviation

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ability of the models to predict poor outcomes in patients with reperfusion failure after EVT (Table 3).

Development and Validation of Modified Prediction Scores

Modified prediction scores were derived by weighting original scores with poor collateral grade based on the results of the linear SVM. Modified HIAT2 (mHIAT2), mTHRIVE, and mPRE scores were obtained by the addition of 3 points, 3 points, and 10 points for poor collateral to the conventional HIAT2, THRIVE, and PRE scores, respectively (Table 1, Figure 2). These modified models were tested by ROC analysis with the validation dataset. The AUC-ROC for the conventional HIAT2, THRIVE, and PRE scores was 0.714, 0.751, and 0.777, respectively, and was 0.781, 0.818, and 0.798 for the mHIAT2, mTHRIVE, and mPRE scores, respectively. The ROC of the modified scoring models was significantly larger than that of conventional models ($P < .001$; **Table**, **Supplemental Digital Content 2**).

The distribution of poor outcomes among the 3 risk groups for modified and conventional scores in validation cohorts is shown in Figure 3. Only high-risk groups showed that the prevalence of poor outcome was constantly higher in the modified models than in the conventional models, differently to low-/intermediate-risk groups.

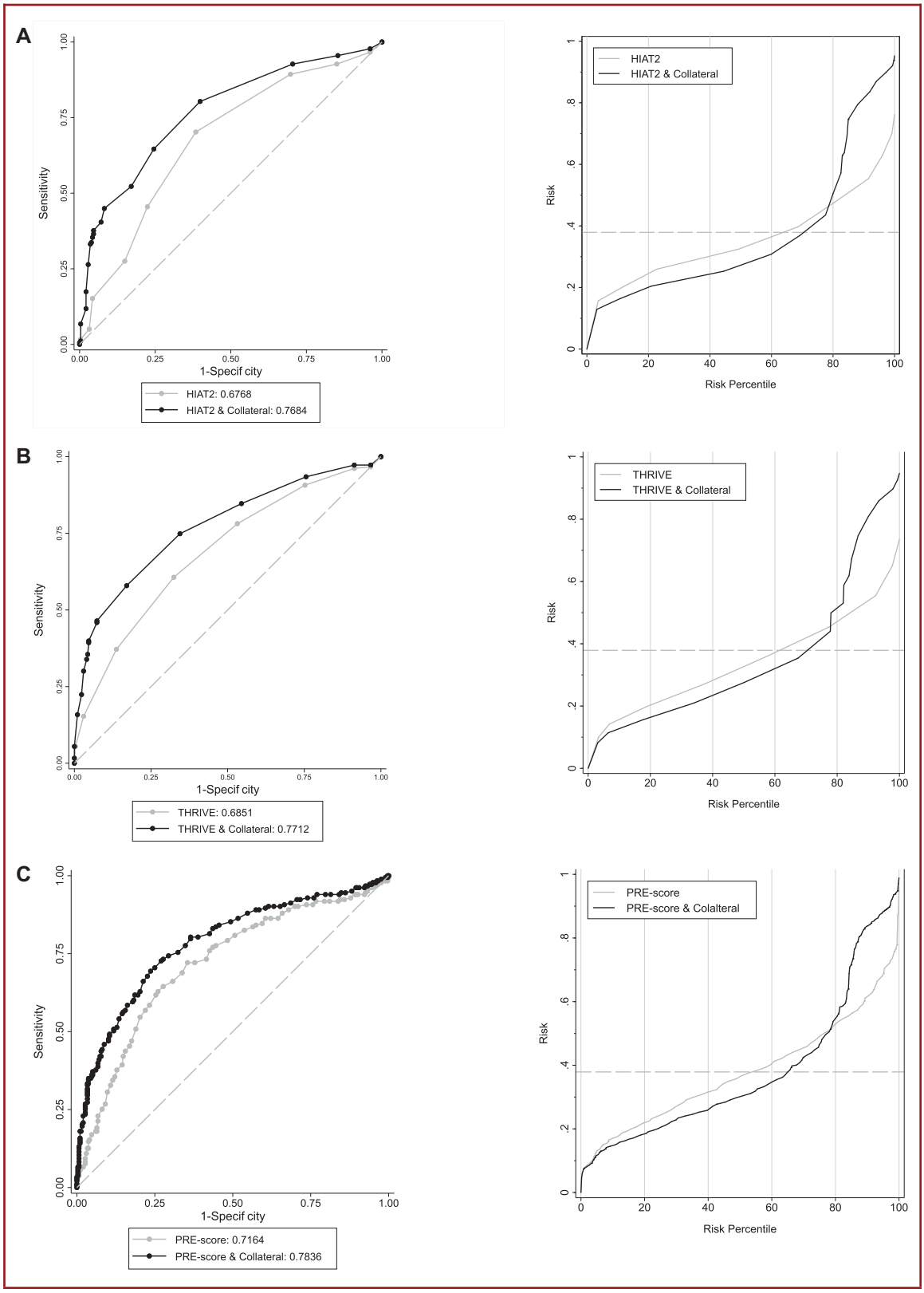
DISCUSSION

In this study, the addition of collateral grade to conventional prediction models increased significantly their predictive for poor outcome in AIS patients treated by EVT, and this effect was consistent regardless of the time-window from symptom onset to EVT. We developed a simple method to add the collateral grade to conventional prediction models using machine learning algorithm. Next, we verified that the three modified scoring models incorporated with collateral grade were a more accurate pretreatment predictor of functional outcome than conventional models in independent validation cohorts. The modified scores can provide an easy-to-use and accurate method to stratify a patient's risk of poor outcome at the time of basic screening using clinical presentation, history, and imaging.

Collateral Circulation in AIC

Two recent randomized trials—DAWN and DEFUSE 3 trials—indicated that, even when the onset of AIS occurs over 6 h prior to intervention, EVT is beneficial for patients in whom salvageable brain tissue is seen by perfusion imaging.[15,16] This suggests that indications for EVT will be shifted from time-window to imaging findings showing a penumbra-infarct core mismatch. The collateral grade measured on CTA is an independent factor related with clinical outcome in AIS. This may be explained by a physiological hypothesis that better collateral circulation status is associated with a smaller ischemic core and higher mismatch, sustaining salvageable tissue in the time-window between onset and treatment.[17,18] Therefore, collateral grade on CTA may be a reliable and less time-consuming alternative to the CT and magnetic resonance perfusion imaging that were used in the DAWN and DEFUSE 3 trials, which require additional efforts or resources for image acquisition.

The role of collateral grade on CTA in suitable patient selection for EVT was confirmed by the ESCAPE trial, which included patients who were treated up to 12 h after symptom onset.[19] The role of collateral grade in terms of clinical decisions was also clarified in a recent study that examined clinical factors affecting outcomes in patients transferred from a referring hospital to a stroke center.[20] This study suggested poor collateral grade is a predictor of an unfavorable imaging profile for thrombectomy during transfer. Similarly, the merit of the present study was



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FIGURE 1. *ROC curves (left column) and predictiveness curves (right column) comparing outcome prediction-scoring models (HIAT2, THRIVE, and PRE scoring systems) with or without collateral grade. The black line represents prediction scores with the addition of collateral grade and the grey line represents prediction scores alone. Left column:* **A**, *The AUC-ROC of the HIAT2 score alone was 0.677 (95% CI, 0.627-0.726), and 0.768 (95% CI, 0.724-0.813) for the HIAT2 score with the collateral grade.* **B**, *The AUC-ROC of the THRIVE score alone was 0.685 (95%CI, 0.685-0.636), and 0.771 (95% CI, 0.727-0.816) for the THRIVE score with the collateral grade.* **C**, *The AUC-ROC of the PRE score alone was 0.716 (95%CI, 0.668-0.765), and 0.784 (95% CI, 0.740-0.827) for the PRE score with the collateral grade. Right column: Graphical representation of the distribution of risk using 3 prediction scores (HIAT2, THRIVE, and PRE scores) with or without the collateral grade. The x-axis represents the risk percentiles, and the y-axis represents the probability of identifying the occurrence of poor outcome. The horizontal line of reference corresponds to the prevalence of poor outcome (39.4%).*

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TABLE 3. Reclassification Ability With Include Collateral Grade on CTA to Three Outcome Prediction Models in Each Group by Time-Window and by Recanalization Status

Category	Observation	AUC of ROC			Continuous NRI (95% CI)	IDI (95% CI)
		Model without collateral grade	Model with collateral grade			
Onset to Procedure						
Within 3 h						
HIAT2 score	157	0.588	0.673	$P < .05$	0.548 (0.234, 0.816)	0.080 (0.010, 0.180)
THRIVE score	171	0.636	0.702	$P < .05$	0.596 (0.315, 0.869)	0.085 (0.015, 0.173)
PRE score	171	0.660	0.710	.093	0.596 (0.309, 0.871)	0.075 (0.014, 0.196)
3 to 6 h						
HIAT2 score	201	0.674	0.789	$P < .05$	0.704 (0.482, 0.917)	0.198 (0.108, 0.296)
THRIVE score	209	0.687	0.812	$P < .05$	0.680 (0.486, 0.912)	0.204 (0.115, 0.301)
PRE score	207	0.741	0.824	$P < .05$	0.680 (0.425, 0.915)	0.176 (0.079, 0.286)
Beyond 6 h						
HIAT2 score	101	0.694	0.788	$P < .05$	0.703 (0.286, 1.035)	0.200 (0.089, 0.342)
THRIVE score	102	0.632	0.717	.05	0.641 (0.161, 1.000)	0.197 (0.096, 0.335)
PRE score	101	0.711	0.780	$P < .05$	0.671 (0.151, 0.988)	0.176 (0.074, 0.300)
Recanalization						
mTICI 0-2a						
HIAT-2	85	0.616	0.675	.32	0.538 (0.262, 0.838)	0.072 (0.005, 0.171)
THRIVE	92	0.680	0.729	.13	0.562 (0.185, 0.844)	0.063 (0.005, 0.163)
PRE score	91	0.699	0.726	.44	0.560 (0.167, 0.851)	0.063 (-0.004, 0.165)*
mTICI 2b-3						
HIAT-2	374	0.667	0.778	$P < .05$	0.700 (0.512, 0.886)	0.162 (0.084, 0.256)
THRIVE	390	0.671	0.774	$P < .05$	0.693 (0.518, 0.889)	0.155 (0.086, 0.249)
PRE score	388	0.726	0.802	$P < .05$	0.693 (0.493, 0.876)	0.136 (0.069, 0.223)

AUC of ROC, area under the receiver operating characteristic curves; IDI, integrated discrimination improvement; NRI, net reclassification improvement

* statistically not significant.

NIHSS, National Institute Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score.

to reify the clinical application of collateral grade on CTA for selection of suitable candidates for EVT.

Prediction Scores for EVT of AIS

HIAT2, THRIVE, and PRE scores were derived from data collected in era lacking solid evidence showing the superiority of EVT over the only proven standard of care. However, the predictive power of these scores was validated using cohorts treated with new generation of clot retriever, such as the SWIFT, STAR, and TREVO-2 trials.[21-23] HIAT-2 and THRIVE scores continued to be a strong independent predictor after controlling for the other known predictors such as time to procedure and recanalization status. These 2 scores were developed to exclude patients predicting poor outcome, although PRE score was focused on the prediction of good outcome. Studies of these conventional scores consistently indicated that patients with high risk can have significantly higher odds of poor outcome even if reperfusion is achieved. In this study, adding the collateral grade consistently elevated the poor outcome predictability of the conventional scores in a fashion that did not interact with the relationship between recanalization and outcome. Furthermore, this modified method was more accurate for discriminating poor

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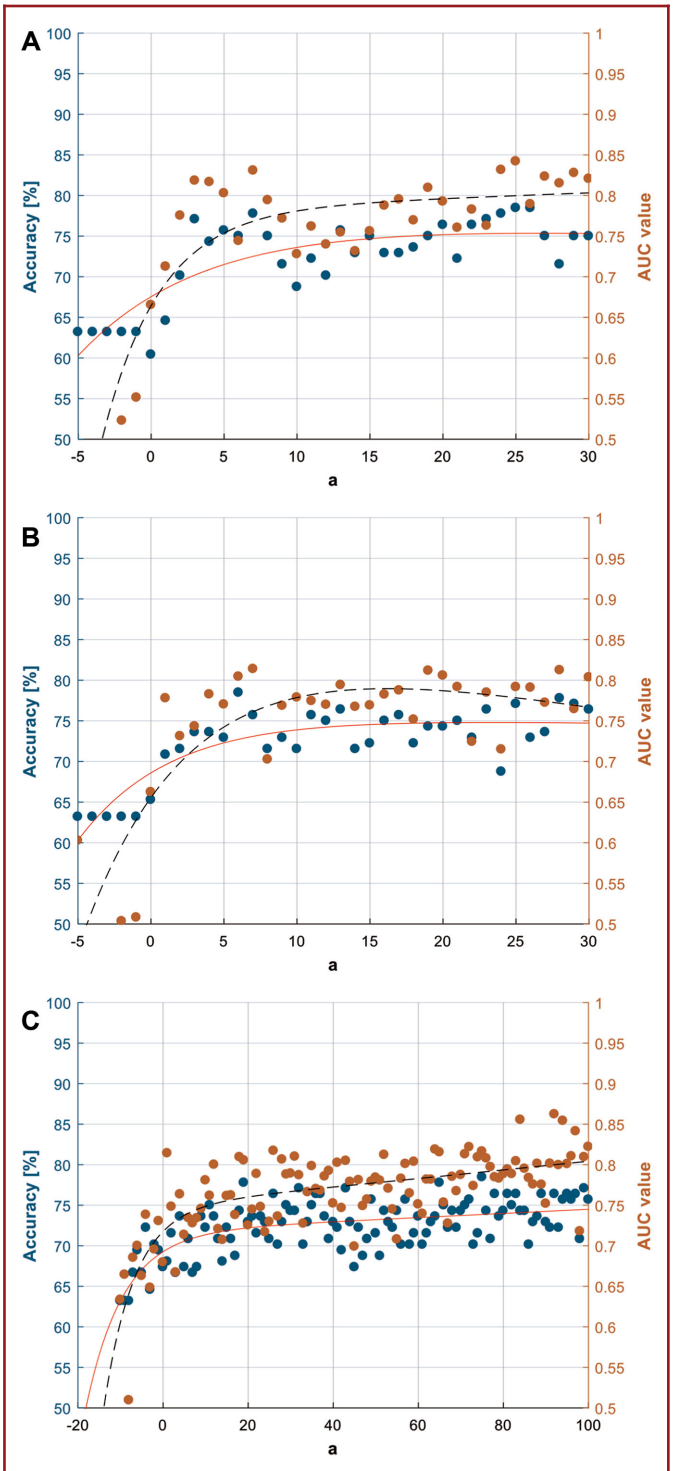


FIGURE 2. *Performance evaluation with various constant value "a" for the poor collateral grade using linear support vector machine method. Overall accuracy and AUC-ROC rise steeply then flatten by the constant value 3, 3, and 10 approximately in* **A**, *HIAT2,* **B**, *THRIVE, and* **C**, *PRE scoring systems, respectively.*

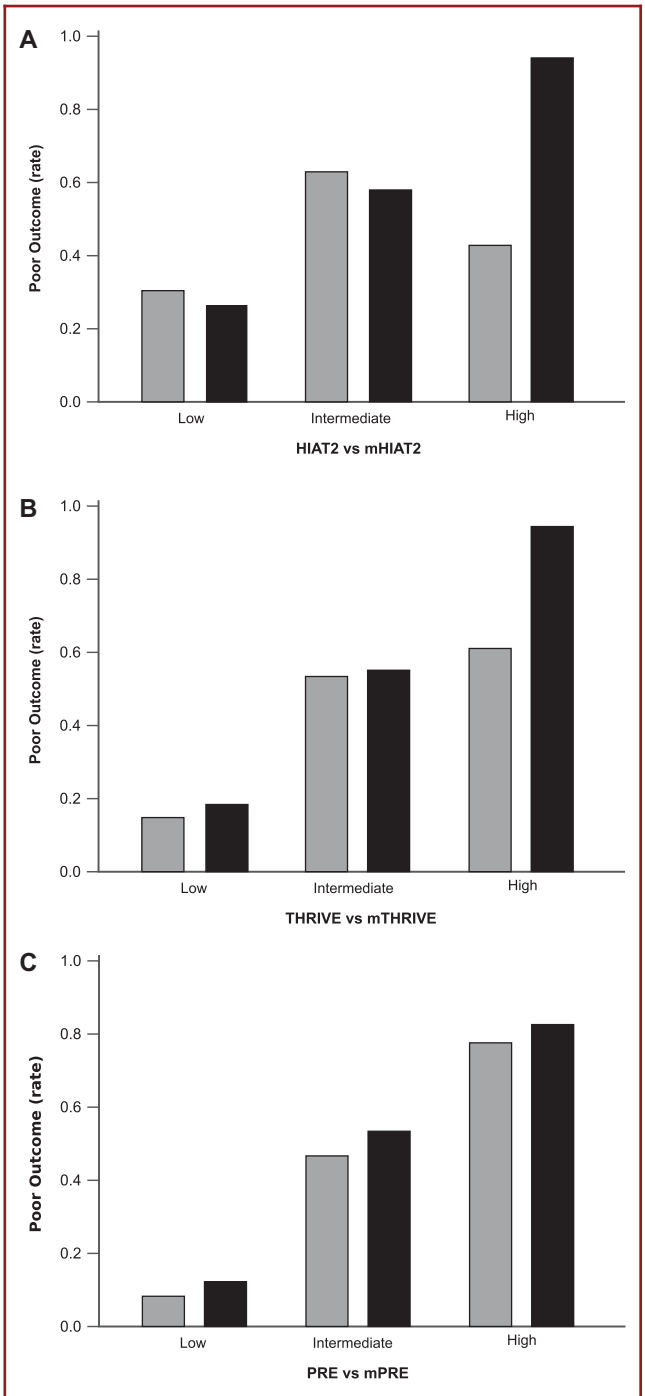


FIGURE 3. *Bar-graph for the prevalence of poor outcome in 3 risk categories (low, intermediate, and high risk) for the validation cohorts. Gray bars indicate conventional prediction scores; black bars indicate modified prediction scores. In every bar-graph, the prevalence of poor outcome in the high-risk group was higher in the modified prediction scores than in the conventional prediction scores.* **A**, *HIAT2 score (low: 0-4, intermediate: 5-7, high: 8-10) and mHIAT2 score (low: 0-5, intermediate: 6-9, high: 10-13).* **B**, *THRIVE score (0-3, 4-6, 7-9) and mTHRIVE score (0-4, 5-8, 9-12).* **C**, *PRE score (<0, 0-50, 50<) and mPRE score (<10, 10-60, 60<).*

outcome in patients who were rated as high risk on this scoring system than patients with low/intermediate risks, as it was shown in the predictiveness curves and bar-graphs.

Every developer of these prediction scores proposed that, because these scores are reliable, simple to administer, and fast to perform, the scores seem to be suitable as treatment decision tools for the AIS with LVO. However, there has not been any prospective study showing the benefit of using these scoring systems to determine patient selection for EVT. Therefore, further prospective studies designed for developing prediction scores modified by collateral grade should be conducted. Especially, the current recommendation of EVT for selected AIS patients who are beyond 6 h of their last known normal implies the need for reliable decision-making tools that are independent of time-window and are based on the imaging of salvageable brain tissue.[1,16,24] Although the mismatch analysis from perfusion imaging validated its role to decide EVT candidates,[15,16] its application may be limited in real practices because of an expensive imaging analysis software and additional effort to acquire the perfusion imaging. In contrast, the modified prediction score in this study simply required CTA, which is the baseline image for acute stroke worldwide, and may present a useful tool in deciding whether to pursue EVT when the perfusion imaging analysis is unavailable. However, this study did not provide enough evidence that modified scoring system helps making treatment decision for the patients with AIS in the recently proven more extended time-window up to 16 h or 24 h, because the time-window for EVT in this study was only limited up to 10 h. Therefore, further study should be conducted to identify the benefit of the modified prediction score in pursuing EVT for the patients with stroke at late time-windows up to 24 h.

Limitations

The present study was derived from a large, retrospective cohort of patients who underwent EVT at multiple centers, allowing a robust analysis of real-world clinical practice. Nevertheless, our study might have a bias related to unadjusted variables stemming from inclusion criteria and treatment options. As suggested in a previous study, multiphase CTA is likely superior to single-phase CTA in collateral status evaluation. The contrast agent filling cerebral arteries can be insufficient on single-phase CTA, due to the delayed circulation time relative to CTA scan initiation in any individual patient. To reduce misclassification of patients with good collateral circulation as having poor collaterals due to delayed cerebral arterial filling, we only included cases when vessel markings in the contralateral normal hemisphere were well visualized. Also, to alleviate the difference between single and multiphase CTA, we only used first-phase images for collateral circulation evaluation in patients who underwent multiphase CTA. Although many studies grading collateral circulation using source images from CTA scored collateral grade on a 4-point scale, according to Maas and colleagues' rating scale[7,25], we simplified the collateral grade scoring system as a 2-point scale, because the 4-point scaling method may have carried the risk of misclassifying patients due to potential variability in CTA protocols between multiple institutes. For better resolution of predicting clinical outcomes, a detailed classification may be better than this dichotomization.

CONCLUSION

The present study proposed that adding collateral grade to convectional prediction-scoring models can strengthen their predictive power for poor outcome after EVT in AIS patients with LVO. The strength of these modified prediction scores is their high predictive value in identifying the patients who would not benefit from EVT despite being a candidate for this procedure. Using them will be useful for excluding unsuitable patients, since the limitation of resource of management or decision of inter-facility transfer, or, conversely, these modified scores may salvage patients who, despite having EVT contraindicated based on their symptom onset-to-procedure time window, may benefit from the procedure. To apply these models in clinical practice, more evidence should be collected by further prospective studies.

Disclosures

This work was supported by a grant from Kyung Hee University in 2016 (KHU-2016069). This research was investigator-initiated and supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare of the Republic of Korea (HC15C1056). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors documented a retrospective multicenter study on the impact of collateral circulation observed on CTA in the clinical outcome of patients with acute ischemic strokes of the anterior circulation undergoing endovascular revascularization. The data was obtained from a retrospective registry of prospectively registered cohorts. The observed collateral grade (good or poor) was added to previously published outcome prediction scores (HIAT 2, THRIVE, PRE) that are based on age, NIHSS, hypertension, diabetes, atrial fibrillation, glucose and ASPECTS scores. Poor collaterals were defined as few or no vessel markings in more than half of the MCA territory. By adding the collateral grade there was statistical superiority in determining the patients with poor outcomes 3 months after therapy based on modified Rankin scales. Collateral grade was an independent factor related with clinical outcome. This may be explained as better collateral circulation associated with smaller ischemic core and higher mismatch. This is important information as CTAs are available in more institutions and are less time consuming than CTP and MRP. A prospective clinical trial studying collaterals on CTA is indicated to evaluate the potential impact on clinical practice.

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Although intra-arterial thrombectomy is now mainstream and widely accepted for many patients with acute ischemic stroke all the way out to 24 hours after symptom onset, outcomes can be highly variable among patients. Therefore, there is a burning need for further refinement of patient selection for thrombectomy.

The authors modified 3 outcome-prediction models for thrombectomy for acute ischemic stroke by adding CTA data on collateral circulation and found the modified prediction models to have superior predictive power. Specifically, human interpretation of collateral circulation to the ischemic territory based on CT angiography was classified as either 'good' or 'poor.' Machine learning was applied to determine optimum coefficients of the modified scores, which were computed as linear combinations of the unmodified score and the binary collateral status. Compared to the original scores, modified scores improved prediction of both clinical and recanalization outcomes. If these findings are validated in further studies, this use of CTA may be of significant value in the management of acute ischemic stroke.

Correlation of collateral circulation with good functional outcome seems intuitive; however, it is interesting to note that the addition of collateral circulation improved prediction of recanalization, which is not intuitive. Whereas the former is a surrogate for perfusion to the penumbra, the latter is – at least superficially – unrelated to collateral circulation but rather is the result of mechanical disruption of a clot. Perhaps patients who have robust collaterals also have different biological characteristics of the intracranial arteries, or even different thrombus properties, compared to patient with poor recanalization, making them more amenable to thrombectomy.

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Supplemental Digital Content 1. Detailed description of study design: Collateral-based reSetting of Endovascular Thrombectomy for acute Stroke retrospective (CoSETS-retrospective) registry. 1. Patient enrollment 2. Data collection and assessment 3. References

Supplemental Digital Content 2. Table. ROC of conventional and modified prediction models for validation data. This table shows the result of the comparison of AUC-ROC between conventional prediction models and modified models for outcome prediction in validation data.

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Folate Receptor Overexpression in Human and Canine Meningiomas—Immunohistochemistry and Case Report of Intraoperative Molecular Imaging

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Received, February 2, 2018.
Accepted, June 12, 2018.
Published Online, August 3, 2018.

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BACKGROUND: Meningiomas are well-encapsulated benign brain tumors and surgical resection is often curative. Nevertheless, this is not always possible due to the difficulty of identifying residual disease intraoperatively. We hypothesized that meningiomas overexpress folate receptor alpha (FRα), allowing intraoperative molecular imaging by targeting FRα with a near-infrared (NIR) dye.

OBJECTIVE: To determine FRα expression in both human and canine meningioma cohorts to prepare for future clinical studies. Present a case study of a meningioma resection with intraoperative NIR fluorescence imaging.

METHODS: Tissue samples of 27 human meningioma specimens and 7 canine meningioma specimens were immunohistochemically stained for FRα along with normal dura, skeletal muscle, and kidney tissue. We then enrolled a patient with a pituitary adenoma and tuberculum sella meningioma in a clinical trial in which the patient received an infusion of folate-linked, NIR fluorescent dye prior to surgery.

RESULTS: In the cohort of human meningiomas, 9 WHO grade I, 12 grade II, and 6 grade III tumors were identified. Eighty-nine percent of WHO grade I, 67% of grade II, and 50% of grade III tumors overexpressed FRα. In the 7 canine meningioma samples, 100% stained positively for FRα. Both human and canine normal dura from autopsy samples demonstrated no evidence of FRα overexpression. In the case study, the meningioma demonstrated a high NIR signal-to-background-ratio of 4.0 and demonstrated strong FRα immunohistochemistry staining.

CONCLUSION: This study directly demonstrates FRα overexpression in both human and canine meningiomas. We also demonstrate superb intraoperative imaging of a meningioma using a FRα-targeting dye.

KEY WORDS: Canine, Folate-receptor, Immunohistochemistry staining, Meningioma, Near-infrared imaging

Neurosurgery 85:359–368, 2019 DOI:10.1093/neuros/nyy356 www.neurosurgery-online.com

Meningiomas are the most common benign brain tumor in adults, accounting for 33.8% of all primary central nervous system tumors diagnosed each year in the United States.[1] Most of these tumors are encapsulated and benign (WHO grade I) but may cause serious problems due to mass effect on critical structures. Atypical (WHO grade II) and malignant (WHO grade III) meningiomas account for approximately 5% to 20% of all meningiomas.[1–3] Surgical resection is the primary mode of treatment for symptomatic meningiomas given their benign nature. However, despite surgery and adjuvant radiation therapy, median time to radiographic progression is 12, 7, and 2 yr for WHO grade I, II, and III meningiomas respectively.[1,4]

Still considered the gold standard for meningioma resection classification, the classic 1957 paper by Simpson,[5] *The Recurrence of Intracranial Meningiomas After Surgical Treatment*, details meningioma recurrence rates as well as a grading system for surgical resection. In short, the more extensive a resection, the less chance for recurrence. This surgical principle continues

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **FRα,** folate-receptor alpha; **H-score,** histo score; **IRB,** Institutional Review Board; **MRI,** magnetic resonance imaging; **NIR,** near-infrared; **SBR,** signal-to-background-ratio

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to guide the neurosurgeon's efforts intraoperatively. As such, various surgeons have attempted to use fluorescent dyes intraoperatively to aid in distinguishing neoplasm from normal brain parenchyma. The 5-aminolevulinic acid-induced protoporphyrin IX (5-ALA), a prodrug in the porphyrin family that facilitates tumor identification, has been of particular interest and was recently FDA-approved for glioma resection. Valdes et al[6] observed fluorescence in 80% of the 15 meningioma patients.[6] Both Morofuji et al[7] and Puppa et al[8] used 5-ALA to identify bone invasion during meningioma surgery. Despite these benefits, 5-ALA fluoresces in the visible light range, which has limited tissue penetration and is hindered by autofluorescence from surrounding tissue. On the other hand, near-infrared (NIR) fluorescence does not suffer from these disadvantages.

Folate is a necessary vitamin for nucleic acid biosynthesis, and thus the proliferative state of the cell determines the rate of folate internalization.[9] Folate receptors are glycosylphosphatidylinositol linked plasma protein that mediate delivery of folate into cells.[10] Folate-receptor alpha (FRα) is overexpressed in ovarian, renal, lung, pituitary, and breast cancers.[11,12] Importantly, FRα can internalize small molecules or protein conjugated to folate, making it an attractive receptor for chemotherapeutic drugs or fluorescent imaging agents.[13] Indeed, van Dam et al[14] first reported use of a folate-fluorescein dye as a means of identifying ovarian cancer intraoperatively, providing proof-of-principle and demonstrating potential benefit.

Meningiomas have been known for decades to express estrogen and progesterone receptors, but folate-receptor expression has not been well studied.[15] Based on prior work by Ross et al[16] on FRα and FRβ expression in tumors suggesting that meningiomas may be an excellent target for intraoperative molecular imaging, we hypothesized that meningiomas overexpress FRα. Here, we report our findings in ex vivo human and canine meningioma specimens as well as a case report of a surgical resection using NIR fluorescence in a human patient.

METHODS

Human Clinical Pathology Samples

A panel of previously resected meningioma specimens was chosen based on histology and study convenience. All patients were enrolled in Institutional Review Board (IRB) approved studies that allow for tissue banking of human specimens with subsequent future deidentified analysis. All surgeries were performed between 2011 and 2016. Demographic and surgical information was queried from the patient's electronic medical records. Cases were selected at random but in such a way as to increase the number of WHO grade II and III cases in our panel. The tumor specimens from each patient were chemically fixed and embedded in paraffin blocks at 5 μm thickness. These permanent sections were stained with hematoxylin and eosin staining. Immunohistochemistry against FRα was performed using murine monoclonal antibodies against the folate receptor (~3.3 μg/mL, NCL-L-FRalpha, Leica, Wetzlar, Germany). Normal human dura from a previous resection was also stained. Human kidney and skeletal muscle (quadriceps muscle) served as positive and negative controls, respectively.

Canine Meningioma Pathology Samples

A panel of previously resected canine meningioma specimens were identified through the Pathology Service at the School of Veterinary Medicine at our institution. Specimens were formalin-fixed and embedded in paraffin blocks at 5 μm thickness. Sections were stained with hematoxylin and eosin. Immunohistochemistry was performed using a rabbit anti FOLR1/FRα antibody (~1.3 μg/mL, LSBio #LS-B5727, Seattle, WA) diluted 1:750 in Antibody Diluent (003118, Life Technologies, Fredrick, Maryland). Normal canine dura was stained. In addition, normal canine kidney and normal skeletal muscle was stained as positive control and negative control, respectively.

Quantification of FRα Expression

In order to quantify the amount of FRα receptor expression, an H-score (or "histo" score) was calculated for each specimen. The H-score ranges from 0 to 300, with 300 implying strong staining in all cells of the specimen. An H-score is designed to give more relative weight to higher-intensity membrane staining in a given specimen. A single neuropathologist at our institution, blinded to all fluorescence data, scored all specimens.

H-Score Calculation for FRα

H-Score = [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)].[16,17] Our cutoff of the H-score to define overexpression is currently arbitrary. The best way to determine the appropriate cutoff would be to determine threshold at which the surgeon could distinguish elevated signal as a function of increasing H-score. Unfortunately, this clinical study is not yet available.

Data Analysis

The data from 27 patients were analyzed using STATA 10^{TM} (StataCorp LLC, Lakeway Drive College Station, Texas). Linear Regression analysis was used to predict the FRα H-score. Independent variables tested included gender, age, body mass index (BMI), tumor diameter, fluid-attenuated inversion recovery sequence on magnetic resonance imaging (MRI), tumor location, history of prior radiation, Ki-67 index, and WHO grade. Image analysis was performed using VisionSense software (VSPlayer, v1.8.05.01, VisionSense, Philadelphia, Pennsylvania) and ImageJ (https://imagej.nih.gov/ij/; National Institute of Health (NIH), Bethesda, Maryland).

Human Case Example

We enrolled a patient with a somatotroph pituitary adenoma in an IRB-approved phase I, open-label pituitary imaging clinical trial using OTL38. OTL38 (OnTarget Laboratories, West Lafayette, Indiana) is a folate-analog linked to a NIR dye IR783.[18] This prospective clinical study was not designed for patients with meningiomas but rather, pituitary adenomas. Preliminary results from this pituitary trial have been published.[19] Because 1 patient also had a tuberculum sella meningioma, the extended endonasal approach provided access to both tumors in the same setting, thus allowing for intraoperative visualization of both the pituitary adenoma and WHO grade I meningioma.

Approximately 3 hr prior to the surgery, the patient received an intravenous 0.025 mg/kg infusion of the study drug over 45 min. A standard, endonasal, endoscopic trans-sphenoidal opening was

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TABLE 1. Description of Patients—Demographics & Tumor Parameters

	ID	Age	Gender	BMI	Prior craniotomy (yr)	Prior radiation (yr)	Location	FLAIR (none, mild, significant)	Maximum tumor diameter (mm)
WHO Grade 1									
	OTL-11	74	F	31.6			Tuberculum sella	Mild	30
	ICG-21	74	M	28			Convexity	Significant	85.4
	ICG-33	64	F	24.7			Sphenoid wing	None	23.9
	ICG-01	32	F	24.4			Olfactory groove	None	15.2
	ICG-513	46	F	34			Convexity	None	33
	ICG-44	52	M	31.9			Olfactory groove	None	42.7
	ICG-29	73	F	19			Parasagittal	Mild	39.8
	ICG-40	64	F	24.5			Convexity		45.2
	ICG-59	54	F	38.4			Sphenoid wing	Mild	24
WHO Grade 2									
	ICG-03	54	F	23	6.8	4.2	Parasagittal	Significant	22.3
	101	66	F	22.8			Convexity	Mild	34.2
	102	58	F	24.2			Parasagittal	Significant	37.2
	103	34	M	27.4			Parasagittal	Significant	44.3
	ICG-42	66	F	30			Convexity	Significant	51.5
	104	73	M	26.3			Convexity	Significant	50.2
	105	68	M	37			Sphenoid wing	Significant	33.9
	ICG-53	68	F	36.7			Parasagittal	Significant	55.5
	106	48	M	24.4			Parasagittal	Significant	30.2
	ICG-55	60	F	35.4	10.5		Sphenoid wing	Significant	53.8
	107	74	M	23.8			Parasagittal	Significant	59.6
	108	54	F	33.6			Parasagittal	Significant	35.6
WHO Grade 3									
	109	64	F	25.5	7.1	6.8	Convexity	Significant	30.5
	110	50	F	27.4			Parasagittal	Mild	28.9
	111	56	F	30.5	1, 1.4	1.2	Convexity	Significant	23.1
	112	89	M	27.1			Convexity	Mild	32.0
	113	80	F	33.1			Convexity	Mild	35.9
	114	74	M	36.5			Parasagittal	Significant	51.3

performed by an otorhinolaryngologist. Upon exposure of the sella, the neurosurgeon employed a NIR-capable camera attached to a 4-mm endoscope to image the tumor before dural opening. The VisionSense Iridium™ (VisionSense) camera's laser excitation light source is tuned to 785 nm, and a dual-light path and sensor design is employed so as to visualize both white light and NIR that can be superimposed in real time. All images with the VisionSense were recorded for posthoc analysis. To quantify the degree of fluorescence, the VisionSense software and ImageJ were used (NIH). Three to five points were placed on the fluorescing samples and surrounding normal tissue to generate a signal-to-background-ratio (SBR). As stated in the informed consent form, the extent of surgery was not modified based on the experimental NIR findings. Surgery proceeded with visible light only, and only upon completion of surgery was the NIR camera reintroduced in order to study margins.

RESULTS

Human Meningioma Specimens

A total of 27 meningioma specimens from patients who had previously undergone meningioma resection (18 females, 9 males; mean age 62 ± 13.3) were studied. Pathology revealed 9 WHO grade I, 12 WHO grade II, and 6 WHO grade III tumors (Table 1). The locations of the tumors were as follows: 10 convexity meningiomas, 10 parasagittal, 4 sphenoid wing, 2 olfactory groove, and 1 tuberculum sella. Four patients had undergone prior craniotomies for tumor resection. Three of those four patients also received radiation following the initial resection. The maximum diameter of the tumors ranged from 15.2 to 85.4 mm (mean: 24.1 mm). The range and mean for the Ki-67 index for the WHO grade I, II, and III meningiomas were 1 to 5 (mean: 2.7), 1 to 18 (mean: 8.5), and 10 to 40 (mean: 26), respectively.

Folate-Receptor Immunohistochemistry Staining

Human kidney (positive control) had an h-score of 180 and human skeletal muscle (negative control) had an h-score of zero. Normal dura demonstrated no expression of FRα, with an H-score of zero (Figure 1). Consequently, we defined overexpression

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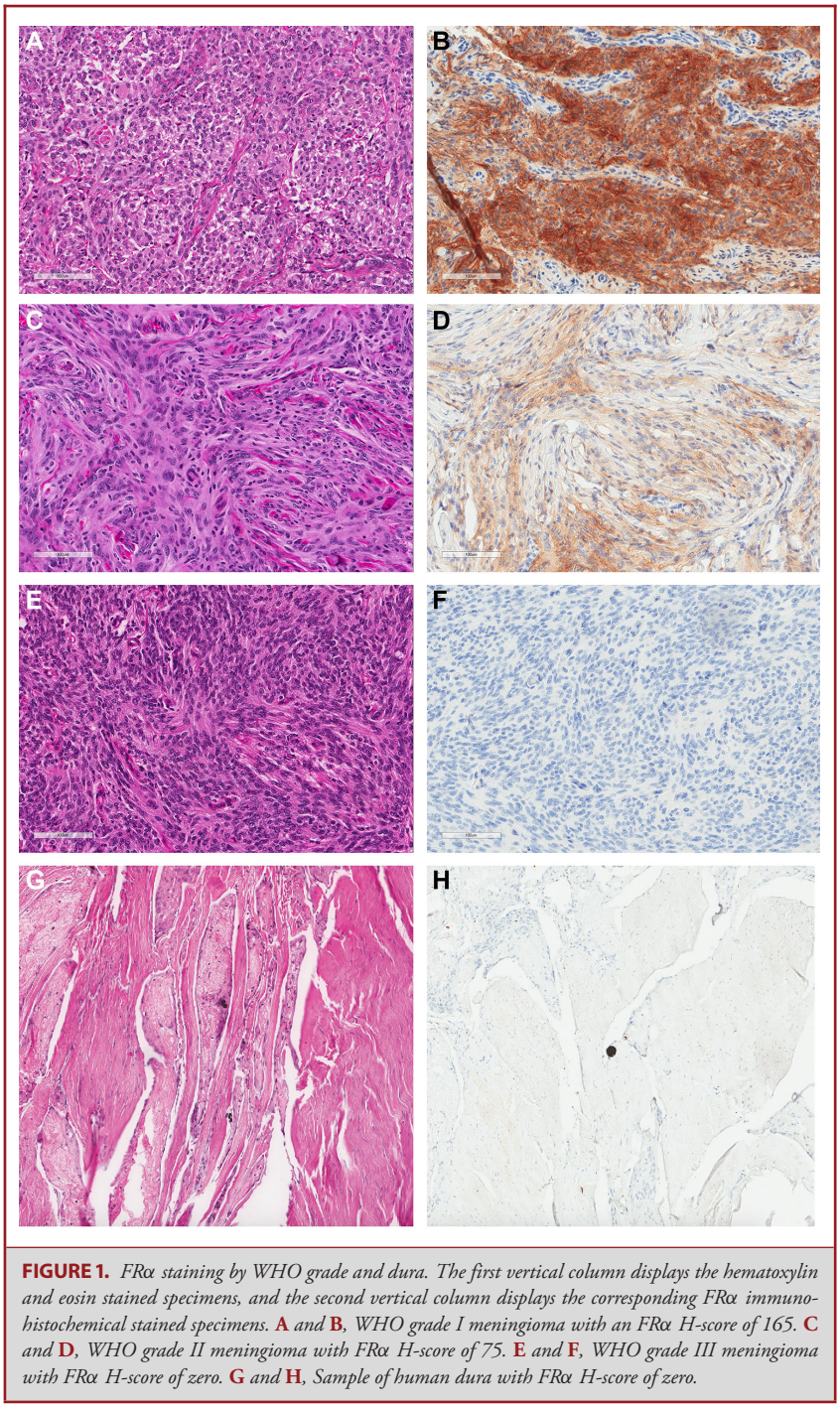


FIGURE 1. *FRα staining by WHO grade and dura. The first vertical column displays the hematoxylin and eosin stained specimens, and the second vertical column displays the corresponding FRα immunohistochemical stained specimens.* **A** *and* **B**, *WHO grade I meningioma with an FRα H-score of 165.* **C** *and* **D**, *WHO grade II meningioma with FRα H-score of 75.* **E** *and* **F**, *WHO grade III meningioma with FRα H-score of zero.* **G** *and* **H**, *Sample of human dura with FRα H-score of zero.*

of FRα in meningiomas as any H-score greater than 10. Eight of the nine (89%) WHO grade I, 8 of the 12 (67%) WHO grade II, and 3 of the 6 (50%) WHO grade III tumors overexpressed FRα (Figure 2). The average H-scores for the WHO grade I, II, and III meningiomas stained were 89.4 ± 67.2, 53.3 ± 62, and 28.3 ± 46.7, respectively (Table 2). The 2 best predictors of FRα overexpression was WHO grade and BMI; increasing WHO grade resulted in a lower likelihood of FRα overexpression ($P = .0575$), while increasing BMI resulted in lower likelihood of FRα overexpression ($P = .0567$).

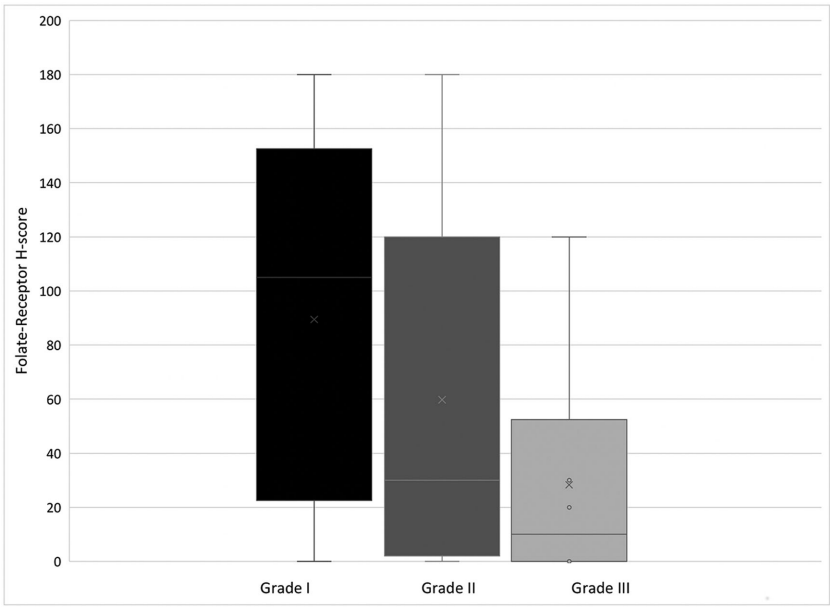


FIGURE 2. *Distribution of human meningioma FRα H-scores. A box plot of FRα H-score on the y-axis for meningiomas in each of the WHO grade categories (x-axis). Overall, higher grade meningiomas expressed lower levels of FRα and had more specimens that expressed no FRα m.*

Seven canine meningioma specimens were immunohistochemically stained for FRα. All 7 (100%) of the canine meningiomas stained positively for FRα with H-scores ranging from 30 to 160 (mean: 96.4 ± 41.5; Table 3). The canine dura and skeletal muscle did not stain for FRα (H-score = 0), whereas the kidney specimen stained positive for FRα with an H-score of 190.

Case Report

A 74-yr-old woman presented with bitemporal hemianopsia, significant weight gain, diabetes mellitus, and enlarging interphalangeal joints. The patient's serum IGF-1 was 480 (reference range 34-245). MRI revealed a heterogeneous, hypoenhancing 1.0 × 1.0 × 0.8 cm mass in the right side of the pituitary gland, as well as a separate 2.2 × 3.0 × 2.0 cm extra-axial suprasellar mass along the tuberculum sellae, presumed to be a meningioma (Figure 3).

Intraoperatively, after removal of the sellar bone and the planum sphenoidale, the NIR camera was set at an appropriate distance that allowed both the meningioma and the adenoma to be captured in the same view. The adenoma fluoresced with an SBR of 2.4 and the meningioma fluoresced with an SBR of 4.0 with the dura intact for both (Figure 3). After the senior neurosurgeon resected the obvious portions of the adenoma, the NIR endoscope was used to visualize the area, revealing a small area with an SBR of 2.7. A specimen was resected from the area and pathology determined it to contain both adenoma and meningioma. Once the pituitary adenoma had been resected, the meningioma was gradually debulked. Once the senior neurosurgeon was satisfied with the resection, the NIR camera was used to establish whether there was any remaining fluorescence at the margins. An isolated area of SBR 3.1 appeared to be emanating from the inferior frontal lobe (Figure 3). This specimen was not believed to be neoplastic by the surgeon's impression but was biopsied; pathology revealed it to be positive for meningioma.

Immediately after resection, the excised specimens were imaged ex vivo, using an exoscope for NIR fluorescence. The adenoma sample fluoresced with an absolute signal of 95 units at a gain of 100% while the meningioma sample fluoresced with an absolute signal of 102 units at a gain of only 11%, for a gain-corrected signal of 927 units (ImageJ, NIH; Figure 4).

Hematoxylin and eosin staining confirmed that the pituitary adenoma was consistent with gonadotroph adenoma. Immunohistochemistry for FRα on the pituitary samples revealed minimal expression of FRα, with an H-score of only 20. Conversely, the meningioma samples stained very intensely for folate receptor alpha, with an H-score of 180 (Figure 4). Based on current WHO criteria, this meningioma sample was consistent with WHO grade I benign meningioma.

DISCUSSION

FRα has the intrinsic ability to internalize folate conjugated to small particles and proteins. Thus, several strategies including anti-FRα-antibodies, drugs conjugated to folate,

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TABLE 2. FRα H-scores in Human Meningiomas

ID	1+	2+	3+	FRα staining H-score	KI-67 proliferation index
Meningioma WHO grade I					
OTL-11	30	60	10	180	2
ICG-21	10	25	35	165	2
ICG-33	20	30	20	140	1
ICG-01	40	40	0	120	4
ICG-513	30	30	5	105	5
ICG-44	20	15	0	50	4
ICG-29	25	0	0	25	3
ICG-40	20	0	0	20	1
ICG-59	0	0	0	0	3
Meningioma WHO grade II					
ICG-03	20	35	30	180	5
101	10	30	20	130	18
102	40	30	10	130	2
103	25	25	0	75	15
ICG-42	50	0	0	50	10
104	30	0	0	30	15
105	20	2	0	24	5
ICG-53	15	0	0	15	1
106	0	0	1	3	5
ICG-55	2	0	0	2	2
107	0	0	0	0	12
108	0	0	0	0	12
Meningioma WHO grade III					
109	25	25	15	120	40
110	30	0	0	30	10
111	20	0	0	20	20
112	0	0	0	0	40
113	0	0	0	0	25
114	0	0	0	0	21
Human dura	0	0	0	0	N/a

TABLE 3. Canine FRα H-Scores

ID	1+	2+	3+	FRα staining H-score
B1220330	20	40	0	100
B1314771	10	20	20	110
B1319032	30	0	0	30
B1410969	15	50	0	115
B1412657	20	10	40	160
B1416273	80	10	0	100
B1606517	20	20	0	60
Canine dura	0	0	0	0
Canine kidney	40	30	30	190
Canine skeletal muscle	0	0	0	0

oncolytic viruses, nanoparticles, T-cells, and imaging compounds have been targeted at cancers overexpressing this receptor.[13] Our group is interested in exploring the capabilities of targeting FRα for NIR imaging in certain intracranial tumors. We have previously demonstrated that pituitary adenomas often overexpress FRα and can be imaged with NIR imaging. In this study, we examined whether meningiomas also overexpress FRα. The level of FRα expression was first measured in human and canine meningioma specimens. Then, based on our findings, we conducted a proof-of-principle study in a patient with a meningioma and performed intraoperative, real-time visualization with our FRα-targeting NIR contrast agent.

Human Meningiomas Demonstrate Overexpression of Folate-Receptor

We analyzed the FRα expression in 27 meningioma specimens at our institution. Overall, 78% of the tumors stained for FRα. We found that 89% of the WHO grade I and 67% of WHO grade II meningiomas overexpressed FRα. We found great heterogeneity in the expression of the receptor across all tumors, with H-scores ranging from 0 to 180 (Figure 2). Using linear-regression analysis, the 2 best predictors of FRα-overexpression were WHO grade and BMI. The positive association between BMI and meningioma has been established in prior studies; the suggested mechanism is that adipose tissue may convert androgens to estrogen via aromatase, driving meningioma growth.[19] We were encouraged by the staining seen in the grade I and II tumors. However, grade III meningiomas failed to show the same pattern. This lack of FRα expression in the WHO grade III malignant meningiomas is unfortunate as this is where we envisioned NIR imaging to be particularly useful in aiding with resection and providing longer progression-free survival. It is not clear why the higher grade meningiomas show reduced FRα expression, but we hypothesize that aggressive tumors demonstrate less differentiation than their more benign variants, leading to reduced FRα expression. With almost all grade I and II meningiomas overexpressing FRα, we believe these tumors would be excellent targets for FRα-targeted NIR imaging. In addition, the dura and normal brain parenchyma demonstrate undetectable FRα expression, thus making background signal less likely.[20,21]

Ross et al[16] quantitated folate receptors on the surface of meningiomas (along with other normal and pathological tissues) by looking at mRNA levels.[16] They then obtained crude plasma membrane preparations from these tissues, subjected them to low pH conditions to remove endogenously bound folates and assayed them for specific binding to [^{3}H]-folate. They found the 6 meningiomas studied to all express folate receptors in varying amounts. The level of FRα mRNA levels expressed in arbitrary units as compared to the negative control ranged from 1.9-77.7. They then looked at the ratio of FRβ mRNA levels to FRα mRNA levels and found the ratio varied from 0.2 to 14.1. The expression of [^{3}H]-folate binding proteins in the meningiomas

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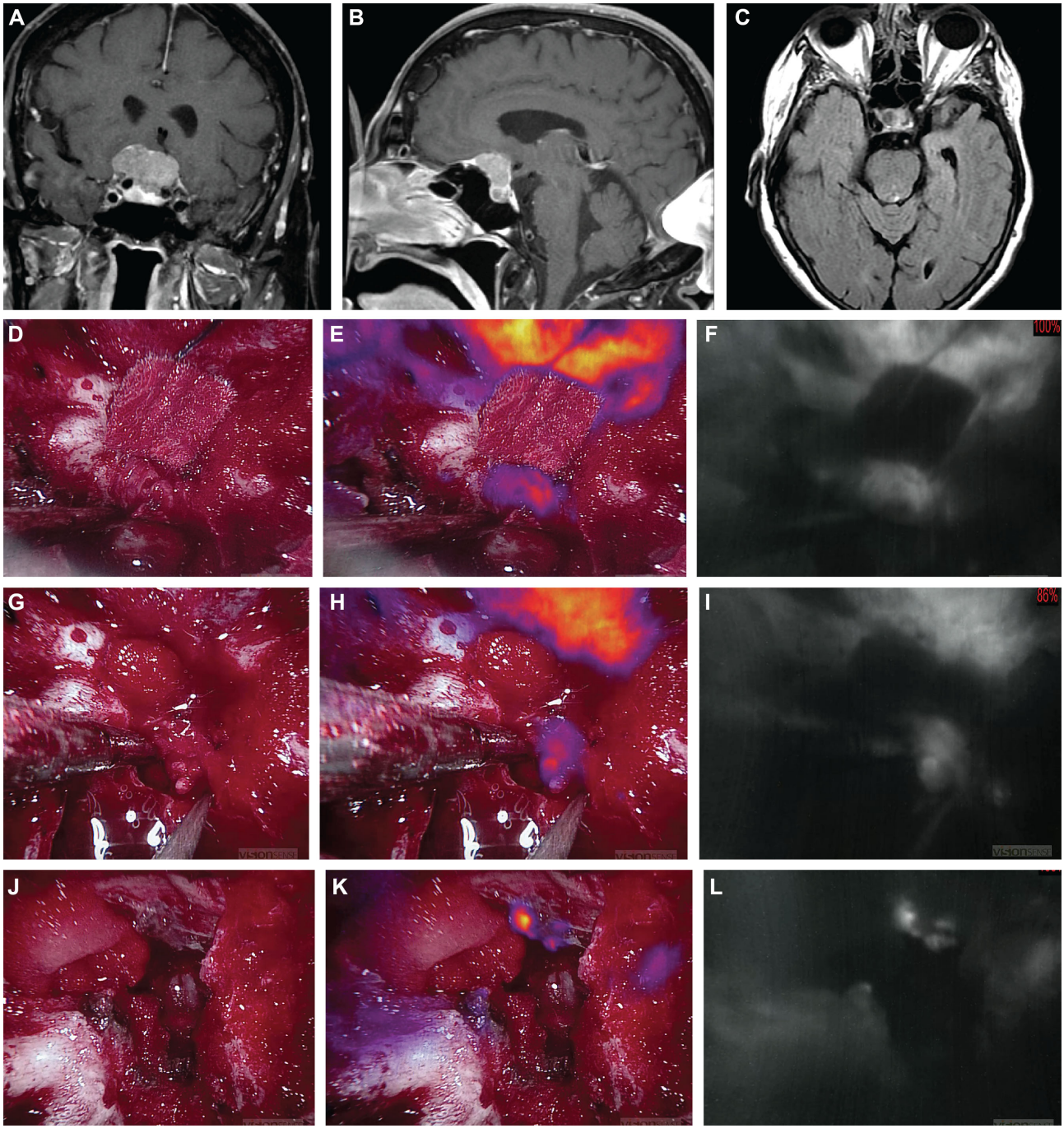


FIGURE 3. *Case example—intraoperative molecular imaging. Each vertical column displays a type of imaging performed by the camera system. The first column displays the visible light image only, the middle column displays the NIR image fused over a visible light image and the third column displays the near infrared only image.* **A-C**, *Preoperative MRI images showing a heterogeneous hypoenhancing 1.0 × 1.0 × 0.8 cm pituitary adenoma in the right side of the pituitary gland, as well as a separate 2.2 × 3.0 × 2.0 cm extra-axial suprasellar meningioma along the tuberculum sellae.* **D-F**, *Intraoperative imaging seen with the dura intact and not yet opened. The NIR signal can be seen localizing just under the dura at the presumed location of the tumor (***E***,* **F***).* **G-I**, *Intraoperative images after the dura is opened; the meningioma is significantly brighter than the pituitary adenoma (***H***,* **I**, *top right corner).* **J-L**, *Intraoperative detection of fluorescent margin from the meningioma that was biopsied and later determined to tumor by pathology.*

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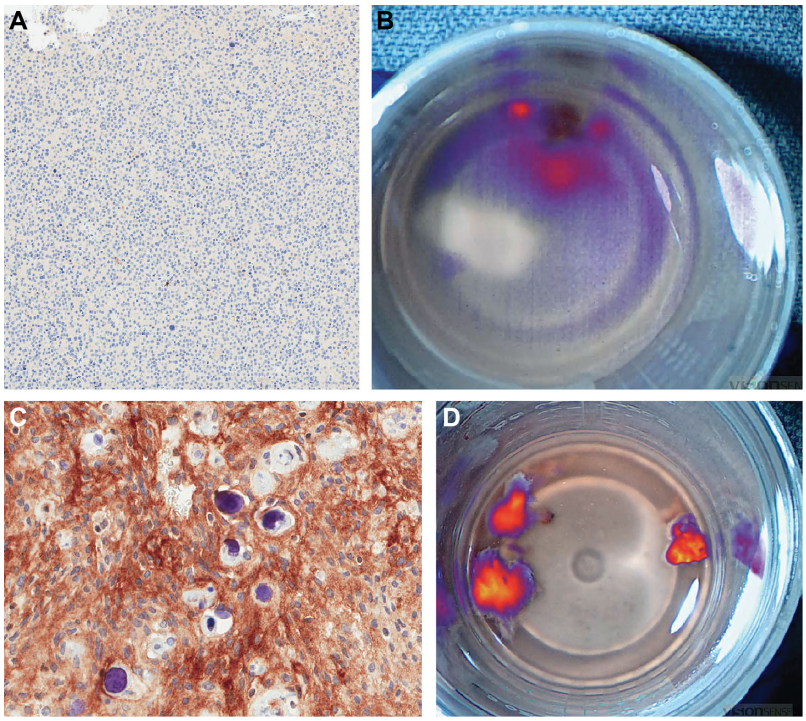


FIGURE 4. *Case example—FRα staining and ex vivo imaging.* **A**, *FRα immunohistochemical staining of the pituitary adenoma specimen demonstrating low H-score of 20.* **B**, *Ex vivo NIR imaging fused over visible light imaging of the pituitary adenoma specimen. The camera gain percent was 100% during this portion of imaging.* **C**, *FRα immunohistochemical staining of the meningioma specimen demonstrating high H-score of 180.* **D**, *Displays the back table, ex vivo NIR imaging fused over visible light imaging of the meningioma specimen. Importantly, the camera gain percent was only 11% during this portion of imaging.*

was 21.0 pmol/mg protein. Thus, they demonstrated a correlation between the level of folate receptor mRNA quantified and the active synthesis of both isoforms into functional folate receptors. Of note, the WHO grade for the 6 meningiomas studied was not given. In agreement with our study, Ross et al[16] found heterogeneous folate receptor expression across the meningiomas studied.

Feasibility of a Canine Model for Meningioma NIR Imaging

We next demonstrated that 7 out of 7 canine meningiomas overexpressed FRα. In comparison to the human meningiomas tested, the canine tumors H-scores averaged slightly higher than the human WHO grade I tumors (96.4 vs 89.4). We also stained a section of normal canine dura for FRα that was negative just as with the human dura. Thus, we were able to demonstrate that canine meningiomas behave similarly to human meningiomas, at least with respect to FRα expression in the tumor and surrounding tissue. This is valuable, as canine models to study NIR fluorescence imaging in meningiomas is now feasible for future studies.

Intraoperative Visualization of a Meningioma using NIR Fluorescence

Finally, we enrolled a patient with both a pituitary adenoma and a meningioma into our ongoing clinical study investigating the use of FRα-targeted NIR imaging in pituitary adenomas. Prior literature has suggested that pituitary adenomas, particularly nonfunctional adenomas, overexpress FRα.[22] This patient happened to also have a tuberculum sellae meningioma, which was scheduled for resection along with the pituitary adenoma, allowing us to observe the utility of FRα-targeted NIR imaging in meningiomas.

The somatotroph adenoma in this patient showed minimal expression of FRα, with an H-score of 20. Accordingly, the adenoma demonstrated weak NIR signal (95 absolute units of fluorescence vs the 927 units for the meningioma). The meningioma, which showed a much stronger signal both in vivo and ex vivo, turned out to have a very high expression of FRα with an H-score of 180. After standard resection, we detected an area of fluorescence in the resection cavity. This specimen was believed to be non-neoplastic tissue by the surgeon's impression

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but was biopsied and confirmed by pathology to be meningioma. On postoperative MRI, a small area of residual neoplasm was detected, consistent with the area of fluorescence we had seen. Thus, we demonstrated that FRα-targeted NIR imaging has a higher sensitivity for neoplastic tissue than the surgeon's impression alone, which is in line with our previous findings in pituitary adenomas. If this finding is replicated in future studies with a larger number of subjects, NIR imaging could potentially enhance intraoperative detection of residual neoplasm, leading to greater gross-total-resection rates and improved patient outcomes. Furthermore, NIR imaging can easily be incorporated into existing operating suites and workflow, unlike intraoperative MRI or other potential methods of increasing tumor sensitivity, by the simple addition of NIR excitation/sensor modules to existing microscopes in many cases or by using a dedicated exoscope/endoscope setup. Thus, NIR imaging has great potential and should be studied further in intracranial tumors.

Limitations

Our study is limited by several factors. This study was designed to examine FRα expression in meningiomas with the larger objective of investigating the use of FRα-targeted NIR imaging to aid in resection. The study involved a relatively small number of patients and the number of WHO grade III samples was limited by the total number of these specimens at our institution.

In addition, this study did not involve immunohistochemistry for FRβ, which may also be expressed in meningiomas. It is possible that OTL38 could cross-react with FRβ, which should be investigated in future studies to avoid potential confusion.

Finally, with the endoscopic approach, there is a learning curve to proper usage of NIR fluorescence. With exoscopes, imaging is simple. However, we have observed that the VisionSense endoscope tends to over-estimate fluorescence near the center of its view compared to the periphery (manuscript currently undergoing review). This can cause false-positive NIR signal reading, as we have described previously in pituitary adenomas.[23] Thus, a certain distance must be maintained between the endoscope and the tumor in order to accurately measure its NIR fluorescence. The proper distance can be estimated by maintaining the medial-opticocarotid-recess spanning less than one-third of the screen.

CONCLUSION

Complete resection of meningiomas remains the gold standard for surgical treatment of meningiomas. Intraoperative molecular imaging techniques to improve surgery for meningiomas is not yet currently available, but based on this preliminary study, we suggest that intraoperative imaging of meningiomas is feasible using folate-receptor-targeting NIR fluorophores.

Because normal dura appears not to express FRα, while 89% of WHO grade I meningiomas and 67% of grade II do, we believe this technique can provide strong tumor/nontumor contrast in real-time. This technique may provide value in neurosurgical patients at high risk of meningioma recurrence.

Disclosures

This work was partially supported by the National Institutes of Health R01 CA193556 (SS), Institute for Translational Medicine and Therapeutics of the Perelman School of Medicine at the University of Pennsylvania (JYKL), and National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000003 (JKYL). Dr Lee owns stock options in VisionSense^{TM}. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Meningiomas are tumors of the central nervous system presumably derived from arachnoid cap cells of the leptomeninges and with possible epithelial and mesenchymal origins. The wide histological and genetic diversity of these tumors bears testimony to that. Abnormality of the NF-2 gene on chromosome 22 is the most frequent change associated with convexity meningiomas but inactivation of a host of other tumor suppressor genes and activation of proto-oncogenes contribute to meningioma initiation and progression. Surgical removal of a meningioma and its dural base and any involved bone remains the optimal strategy to treat these tumors. Single fraction or fractionated radiation therapy also has a role in the management of surgically inaccessible or progressive higher-grade meningiomas. Most convexity meningiomas are easily accessible; cranial base or other deeper location tumors are more challenging but skilled surgeons can inflict a significant removal in almost half these cases as well. Visualization of the tumor itself is not hard; it has a fleshy yellowish-brown appearance in most cases that is distinct from surrounding brain and frequently an arachnoid plane around the tumor lends itself to a better resection. The involved dura and bone, which is frequently hyperostotic, is a different challenge. While visual inspection of the dura and intraoperative neuronavigation is helpful in guiding the extent of dural resection, a fluorescent dye that can stain abnormal dura would be ideal.

For neurosurgeons, intraoperative fluorescent imaging provides objective, real-time visualization of diffuse or encapsulated intracranial tumors during surgery. Judiciously used, it allows for more complete resection of the tumor - and possibly better outcome. Passive fluorescent probes such as fluorescein sodium or indocyanine green (ICG) or metabolic probes such as 5-aminolevulinic acid (5-ALA) have emerged as the predominant agents used for brain tumor resections although numerous other fluorophores await development and approval.[1] Most of these probes have the ability to accumulate in tumor tissue - large molecular weight or non-lipophilic probes rely on defects in the blood brain barrier to facilitate their accrual. The optical modalities are important as well - photons with a longer wavelength in the near-infrared spectrum have greater tissue penetration and sensitivity to tumor tissue.[1] For intracranial neoplasms, 3 predominant fluorescent contrast agents have emerged; fluorescein sodium, ICG, and 5-ALA. We have had cautious optimism with the use of fluorescein sodium in the resection of malignant gliomas, meningiomas, and metastatic brain tumors - as previously reported by other groups.[2] The agent is easily administered by intravenous injection following induction of anesthesia and visualization under the yellow-560 module facilitates tumor visualization as a bright-green fluoroscence. Specificity and quantification of the degree of fluorescence remains a challenge and can be affected by various factors such as absorption, scatter, anisotropy, and autofluoroscence.[1]

This manuscript describes a targeted probe that was being evaluated for the resection of pituitary adenomas and that was incidentally found to have a use for meningioma resection. The folate-receptor alpha (FRα) probe (OTL-38), described in this manuscript, is a targeted probe with the potential to isolate neoplastic meningothelial cells. OTL-38 has been used with ovarian and lung cancer resections and is a targeted agent with excellent penetration and low local tissue autofluorescence.[3,4] The authors expanded their study to a tissue bank of human and canine meningiomas and report robust FRα expression in benign WHO grade 1 cranial meningiomas, while FRα expression was lacking in normal dura. They suggest this might serve as a novel target for intraoperative visualization of the tumor and its dural base facilitating more complete resections of intracranial, and potentially spinal, meningiomas.

As such, there does not appear to be a clear linkage between FRα expression and the precise embryological lineage of neoplastic cell lines. It is seen in benign and malignant neoplasms of ectodermal or mesodermal origin - thus, it may simply be a reflection of dysregulated cellular metabolism. FRα is overexpressed in pituitary tumors, and certain glioma cell lines.[5] These authors have previously demonstrated the ability to image pituitary adenoma FRα expression with near-infrared imaging.[6] That has great potential benefit particularly in small ACTH-secreting microadenomas in Cushing's disease or to facilitate more complete resections of larger macroadenomas. For meningiomas, the World Health Organization (WHO) grade 1 tumors appear to have the best expression of FRα. One would expect increased FRα expression with increasing grades of meningiomas but WHO grade II and III meningiomas in this series had progressively less expression. Also, no clear correlation was noted between FRα expression and meningioma subtypes although meningothelial and transitional meningiomas were predominant in this series. Whether expression of FRα has the same prognostic inference as the presence of progresterone receptors in meningiomas remains to be seen. It does however, have the potential to facilitate better resections of meningiomas and numerous studies have validated the impact of complete surgical resection on reducing the progression or recurrence-free survival and overall survival of patients with intracranial meningiomas. If an agent can be easily administered and has the ability to improve visualization of the tumor target, facilitate resection and impact outcome without a significant risk of side-effects, then clearly it is worthy of consideration - OTL-38 appears to meet these criteria. It will likely mature over time with gathered experience and neurosurgeons will determine for themselves whether its impact on the quality of tumor resection is significant.

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CNS Spotlight

Quantifying Real-World Upper-Limb Activity Via Patient-Initiated Movement After Nerve Reconstruction for Upper Brachial Plexus Injury

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Received, January 29, 2018.
Accepted, June 21, 2018.
Published Online, July 27, 2018.

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BACKGROUND: A critical concept in brachial plexus reconstruction is the accurate assessment of functional outcomes. The current standard for motor outcome assessment is clinician-elicited, outpatient clinic-based, serial evaluation of range of motion and muscle power. However, discrepancies exist between such clinical measurements and actual patient-initiated use. We employed emerging technology in the form of accelerometry-based motion detectors to quantify real-world arm use after brachial plexus surgery.

OBJECTIVE: To evaluate (1) the ability of accelerometry-based motion detectors to assess functional outcome and (2) the real-world arm use of patients after nerve transfer for brachial plexus injury, through a pilot study.

METHODS: Five male patients who underwent nerve transfer after brachial plexus injury wore bilateral motion detectors for 7 d. The patients also underwent range-of-motion evaluation and completed multiple patient-reported outcome surveys.

RESULTS: The average age of the recruits was 41 yr (±17 yr), and the average time from operation was 2 yr (±1 yr). The VT (time of use ratio) for the affected side compared to the unaffected side was 0.73 (±0.27), and the VM (magnitude ratio) was 0.63 (±0.59). VT strongly and positively correlated with shoulder flexion and shoulder abduction: 0.97 ($P = .008$) and 0.99 ($P = .002$), respectively.

CONCLUSION: Accelerometry-based activity monitors can successfully assess real-world functional outcomes after brachial plexus reconstruction. This pilot study demonstrates that patients after nerve transfer are utilizing their affected limbs significantly in daily activities and that recovery of shoulder function is critical.

KEY WORDS: Accelerometry, Arm use, Brachial plexus, Functional outcome, Patient-initiated assessment, Shoulder

Neurosurgery 85:369–374, 2019 DOI:10.1093/neuros/nyy335 www.neurosurgery-online.com

The goal of every surgical procedure is to achieve a successful outcome. This is true with brachial plexus reconstruction surgery; however, the definition of a successful outcome to this procedure continues to evolve. Current outcomes assessment is based on clinician-elicited measures in the outpatient clinic (eg, muscle strength using the Medical Research Council [MRC] grading criteria, active range of motion [AROM], and video/pictorial recordings). These measures do not assess real-world use of the reconstructed arm.

Subjective patient input regarding the perception of surgical outcome via various surveys that define "patient-reported outcomes" can augment the assessment of outcome. The World Health Organization (www.who.int/classifications/icf) emphasizes the evaluation of the "Activity and Participation" domains (versus clinician-elicited measures in the "Body Function and Structure" domains); however, these subjective disability surveys generally rely on questions assessing the ability

ABBREVIATIONS: AROM, active range of motion; **DN4,** Douleur Neuropathique 4 questionnaire; **IPAQ,** International Physical Activity Questionnaire; **MRC,** Medical Research Council; **PROM,** passive range of motion; **PROMIS,** Patient-Reported Outcomes Measurement Information System; **QuickDASH,** shortened Disability of Arm, Shoulder, and Hand questionnaire; **SPADI,** Shoulder Pain and Disability Index; **VM,** magnitude ratio; **VT,** time of use ratio

to perform global tasks and thus provide little insight into outcomes specific to a surgically reconstructed upper extremity. Hence, the applicability of our current outcomes assessments to the "real-world" use of the reconstructed arm—beyond the exam room—is controversial, and true assessment of arm use in everyday activities remains elusive.

Recent advances in body-worn sensor technology provide a promising improved method for assessing outcomes after brachial plexus reconstruction surgery by quantifying patient-initiated arm movement in remote settings: for example, wrist-worn accelerometers have been used successfully to monitor changes in arm function in chronic stroke.[1] In this novel application of accelerometry to assessing true outcomes after nerve reconstruction for brachial plexus injury, we present the results of a pilot study demonstrating the applicability of accelerometry to evaluate arm use after nerve reconstruction and examine the relationship between patient-initiated real-world arm use and our current clinician-elicited assessment methods.

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METHODS

Study Design

This prospective pilot case series recruited 5 adults with upper brachial plexopathy who underwent nerve transfer procedure in a single institute in 2014 and 2015. The participants completed surveys regarding patient demographics, pain, Patient-Reported Outcomes Measurement Information System (PROMIS), and patient-reported upper extremity function at the study visit. One of two certified occupational therapists conducted standard clinician-elicited physical measurements at the same visit. Participants then wore an activity monitoring device on both the injured (after nerve reconstruction) and noninjured arms for 7 d. The devices were returned at the end of the study for data analysis. Participants were financially compensated for their participation. The study protocol was approved by the Institutional Review Board (HUM103135); informed consent was acquired from all patients prior to study participation.

Accelerometry

Activity monitors (GT9X Link ActiGraph; ActiGraph LLC, Pensacola, Florida) were worn on each wrist during waking hours for 7 consecutive days, of note the patients did not participate in physical therapy during testing. These devices have been shown to be a valid and reliable means of monitoring movements of the upper extremity in motor impairments following central nervous system insult, including stroke[1,2] and cerebral palsy.[3] Each device contains a solid-state accelerometer that records raw acceleration in 3 axes at 30 Hz and can store data locally for up to 14 d. Devices were calibrated prior to use and were attached to the wrist using adjustable watch bands. Accelerometry data were downloaded and filtered using commercial software (ActiLife v6.13.3; ActiGraph LLC). This software was also used to visually inspect data to ensure that participants followed the established protocol for wearing the devices during waking hours over the 7-d period.

Analysis of arm acceleration followed methods previously reported[4] and focused on the amount of time per day that the devices detected movement (VT) and vector magnitude (VM). The latter is a measure of the intensity of upper extremity activity, where, for each second of data, accelerations in the 3 planes of motion were combined into a single vector magnitude value. To compare the daily contribution of each arm to overall time of use and vector magnitude, time and magnitude ratios were calculated by dividing values associated with the affected limb by unaffected limb values.

Demographic and Clinical Measures

Patient demographics included age, surgery to study duration, gender, race, involved side, and dominant hand. Active and passive range of motion (AROM and PROM) of shoulder flexion, shoulder abduction, shoulder extension, shoulder external rotation in adduction, shoulder internal rotation in adduction, elbow flexion in adduction, elbow extension, and forearm supination were measured, as these joints are targeted for functional recovery in patients with upper brachial plexopathy.

Patient-Reported Pain, Upper Extremity Function, and Physical Activity Measures

Pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire and the Shoulder Pain and Disability Index (SPADI). The DN4 is a 10-item questionnaire commonly used to assess neuropathic pain. It comprises 7 patient-reported measures of pain quality and 3 items based on clinical examination. Scores range from 0 to 10, with scores above 4 indicative of neuropathic pain.[5] The 13-item self-report SPADI comprises 2 subscales: pain and disability. Patients are asked to rate the amount of pain experienced during different activities and the degree to which they are impaired by their injury or condition. Subscale scores range from 0 to 100, with 0 indicating no pain or difficulty and 100 indicating worst pain imaginable and help needed because of the injury. Scores are combined and range from 0 (best) to 100 (worst).[6]

Upper extremity function was self-reported using the shortened version of the widely used Disability of Arm, Shoulder, and Hand (QuickDASH). It is validated for a wide range of musculoskeletal conditions and includes 11 items scored 1 to 5. Total scores are calculated, with the highest score of 100 indicating the greatest amount of disability.[7] Manual ability was assessed using 1 of 5 validated ABILHAND questionnaires that measure the ability of specific clinical populations to perform activities of daily living using the upper extremity.[8] The ABILHAND questionnaire designed for stroke was chosen since it focuses primarily on bimanual activities. It consists of 23 items using a 3-level scale from impossible (0), difficult (1), or easy (2). An online Rasch analysis is used for scoring, with lower scores (0-42) indicating greater disability.[9]

Self-reported physical activity was measured using the International Physical Activity Questionnaire (IPAQ). The IPAQ is a validated and reliable assessment of physical activity measured across four domains: occupational, transport, domestic, and leisure.[10] Participants reported their physical activity in hours over the preceding 7 d, with higher scores indicative of greater physical activity. Participants were then classified (low, moderate, or high) based on their scores.

Quality of Life

PROMIS is a generic measure of health-related quality of life that can be applied to the general population and patients with neurological conditions (http://www.nihpromis.org). We reported fatigue, informational support, emotional support, anxiety, anger, and depression domains in this study.

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TABLE 1. Patient Demographic Data

	n (%) n = 5
Mean age (y) ± standard deviation (SD)	41 ± 17
Time from operating room to study (y) ± SD	2 ± 1
Sex	
Male	5 (100%)
Race	
Caucasian	5 (100%)
Involved side	
Left	2 (40%)
Right	3 (60%)
Dominance	
Right	5 (100%)
Lesion type	
Brachial plexopathy	5 (100%)

Statistical Analysis

We assessed descriptive statistics for patient demographic data and ActiGraph data. Pearson correlation was applied to investigate the relationship between ActiGraph arm use data and physical measurements, patient-reported pain, upper extremity functionality, and PROMIS. $P < .05$ was considered as statistically significant. Commercially available software was used for all analyses (SPSS version 22; IBM Corporation, Armonk, New York).

RESULTS

Five patients were recruited for this pilot study. All 5 (100%) patients had nonrecovering brachial plexus injuries for which surgical nerve reconstruction was recommended. The mean age was 41 yr (±17 yr) at the time of surgery, and the average time from surgery to the inclusion of the study was 2 yr (±1 yr). All 5 (100%) patients included in this study were white males. Three (60%) of the injuries were right sided, and 3 (60%) of the injuries involved the dominant arm (Table 1). Patient 1 underwent C5 to posterior division, spinal accessory to suprascapular transfer, and median to musculocutaneous, and patients 2 to 5 all underwent triple transfer repairs (spinal accessory to suprascapular, radial to axillary, and ulnar to musculocutaneous). Shoulder flexion AROM and shoulder abduction AROM ranged from 10 to 160 and 0 to 160, respectively. MRC grading for shoulder flexion and shoulder abduction ranged from 0 to 4- in both. Elbow flexion AROM ranged from 0 to 150, and MRC ranged from 2 to 4-.

The VT reflects the ratio of movement in the injured (reconstructed) arm to the unaffected arm: VT averaged 0.73 (±0.27) over the entire cohort. The range for VT was 0.53 to 1.19. The VM averaged 0.63 (±0.59). The range for VM was 0.23 to 1.66 (Table 2). There was a positive correlation of VT with shoulder flexion and shoulder abduction: 0.97 ($P = .008$) and 0.99 ($P = .002$), respectively. No statistically significant correlation was noted between VT and elbow flexion (0.73, $P = .17$) or forearm supination (0.43, $P = .47$; Table 3). There was a positive correlation of VM with shoulder flexion and shoulder abduction: 0.93 ($P = .022$) and 0.96 ($P = .009$), respectively. Again, no statistically significant correlation was found between VM and elbow flexion (0.66, $P = .23$) or forearm supination (0.39, $P = .52$; Table 3). Both the percentage time of use and the magnitude of movement demonstrate that nerve reconstruction conveys adequate patient-initiated arm use.

TABLE 2. The Percentage of Time of Use and Magnitude of Movement Demonstrate That Nerve Reconstruction Conveys Adequate Patient-Initiated Arm Use

Patient	Time of use ratio (VT)	Magnitude ratio (VM)
1	0.53	0.23
2	1.19	1.66
3	0.62	0.41
4	0.56	0.33
5	0.75	0.5
Total mean ± SD (percentage of unaffected arm)	0.73 ± 0.27 (73%)	0.63 ± 0.59 (63%)

Self-reported pain scales were used for correlations with the activity ratios (VT and VM). There was a positive correlation between the DN4 score and VT (0.96, $P = .011$); however, there was no correlation between the SPADI pain score and VT (0.31, $P = .61$; Table 4). Likewise, there was a positive correlation between the DN4 score and VM (0.94, $P = .018$), but no correlation between the SPADI pain score and VM (0.21, $P = .73$; Table 4). Therefore, pain assessment methods that measure neuropathic pain were more valuable for outcome assessments than general pain measures.

Functional disability scales were used for correlations with arm use ratios. The correlations between QuickDASH and VT and VM arm use ratios were −0.90 ($P = .039$) and −0.86 ($P = .061$), respectively. The statistically significant correlation between QuickDASH and arm time use ratio can be interpreted as patients with higher VT consider themselves to have better upper extremity function. The correlations between ABILHAND score and VT and VM were 0.91 ($P = .033$) and .92 ($P = .025$), respectively. There were no significant correlations between VT or VM and SPADI disability scores or the IPAQ scores (Table 4). Therefore, patient-reported outcomes that are directed at arm and hand use are more relevant than general subjective activity surveys.

The arm use ratios were also correlated with the PROMIS scores (Table 5). There was a correlation between the fatigue subscore and VT and VM, −0.95 ($P = .014$) and −0.97 ($P = .006$), respectively. However, the informational support, emotional support, anxiety, anger and depression subscores showed no significant correlations with either VT or VM.

DISCUSSION

Traumatic injury to the brachial plexus is a devastating event for the adult patient, resulting in decreased function of the upper

TABLE 3. Pearson Correlations With PROM/AROM: VT and VM Correlate With Shoulder Flexion and Shoulder Abduction

	Time of use ratio (VT)				Magnitude ratio (VM)			
	AROM correlation	*P* value	PROM correlation	*P* value	AROM correlation	*P* value	PROM correlation	*P* value
Shoulder flexion	0.97	**.008**	0.52	.38	0.93	**.022**	0.60	.29
Shoulder abduction	0.99	**.002**	0.47	.43	0.96	**.009**	0.39	.52
Shoulder extension	0.48	.41	0.41	.49	0.51	.38	0.38	.53
Shoulder external rotation adduction	0.73	.17	0.42	.48	0.61	.28	0.32	.60
Shoulder internal rotation adduction	0.41	.49	0.68	.21	0.38	.53	0.66	.22
Elbow flexion in adduction	0.73	.17	0.53	.36	0.66	.23	0.47	.42
Forearm supination	0.43	.47	0.41	.49	0.39	.52	0.38	.53

AROM and PROM, active and passive range of motion. Bold *P* value indicates significance.

TABLE 4. Pearson Correlations With Patient-Reported Pain and Upper Extremity Functional Disability: Pain Assessment Methods (DN4) That Measure Neuropathic Pain Are More Valuable for Outcome Assessments Than General Pain Measures

	Time of use ratio (VT)		Magnitude ratio (VM)	
	Correlation	*P* value	Correlation	*P* value
Pain				
DN4	0.96	**.011**	0.94	**.018**
SPADI pain	0.31	.61	0.21	.73
Functional disability				
QuickDASH	− 0.90	**.039**	− 0.86	.061
ABILHAND	0.91	**.033**	0.92	**.025**
SPADI disability	− 0.43	.47	− 0.43	.47
IPAQ MET min/wk	0.70	.19	0.58	.31
IPAQ category	− 0.35	.56	− 0.28	.65

DN4, Douleur Neuropathique 4 questionnaire; SPADI, Shoulder Pain and Disability Index; QuickDASH, shortened Disability of Arm, Shoulder, and Hand questionnaire; IPAQ, International Physical Activity Questionnaire. Bold *P* value indicates significance.

TABLE 5. Pearson Correlations With PROMIS: Fatigue Correlates With Decreased Patient-Initiated Arm Use

	Time of use ratio (VT)		Magnitude ratio (VM)	
PROMIS	Correlation	*P* value	Correlation	*P* value
Fatigue	− 0.95	**.014**	− 0.97	**.006**
Informational support	− 0.18	.77	− 0.07	.92
Emotional support	0.43	.47	0.39	.52
Anxiety	0.12	.85	0.25	.69
Anger	− 0.14	.82	− 0.16	.80
Depression	− 0.44	.46	− 0.47	.43

PROMIS, Patient-Reported Outcomes Measurement Information System. Bold *P* value indicates significance.

extremity.[11] Fortunately, the treatment of brachial plexus injury has advanced dramatically over the past 25 yr.[11] Brachial plexus surgeries, including nerve grafting and nerve transfers, have given hope to a once dismal prognosis.[12] Until now, the focus of research has been on the surgical techniques and therapeutic approaches, but little has been done to further refine the evaluation of these patients.

Evaluating patients with brachial plexus injuries requires serial clinical examinations as well as electro-diagnostic testing with electromyography and nerve conduction studies. Though this focused testing allows us to evaluate each muscle and joint individually, understanding the functional arm use once the patient leaves clinic remains elusive. Attempts to understand the real-world use of the arm have been limited to patient recall and various surveys. This project attempted to not only capture patient-initiated movement, but also to quantify the frequency and quality of the movement through the use of bilateral upper extremity accelerometers. These devices successfully captured and quantified the timing and magnitude of arm movements over the course of 7 d, and showed that patients used their affected arm up to 73% as much as the time they used their unaffected arm and with approximately 63% of the magnitude of movement after a brachial plexus reconstruction. These data on the remote capture of patient-initiated movements are critical in describing the real-world use of the upper extremities. Additionally, these are the first quantifiable data demonstrating how patients do when they leave the clinic, and the results are quite promising. These findings add to the ever-increasing base of knowledge that brachial plexus reconstruction is creating favorable outcomes in our patients.

Brachial plexus functional outcomes are not the only condition in which out-of-clinic evaluations are useful. Cardiac arrhythmias and sleep disturbances are among other conditions where prolonged observation is important. Though the idea of take-home technology may be daunting, holter monitors and at-home sleep studies have been widely and successfully adopted in

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cardiology and sleep medicine. The accelerometry devices that we employed are small wristwatch-like detectors that are much simpler and less intrusive than holter monitors and at-home sleep studies.

Prior to capturing patient-initiated movement with motion detectors, we focused our evaluations on multiple domains: AROM, MRC, patient satisfaction, and patient reporting.[13,14] Although these domains have been widely used, their relationships to one another have demonstrated conflicting messages. For instance, Franzblau et al[15] and Rasulić et al[16] demonstrated that there appeared to be no correlation between clinician-elicited outcomes and patient satisfaction. The apparent disconnect between objective clinical outcomes like MRC grading and subjective clinical outcomes such as patient satisfaction should raise concern that we may be missing the mark in evaluating one or both.

Although widely used and often the main focus of clinical evaluation and research, the utilization of AROM and MRC in the evaluation of these patients has major pitfalls. These outcome measures test single joints and the movements are not patient initiated. As the main goal of surgery is to restore a limb for use in everyday activities, it is a concern that clinical evaluation focuses on two characteristics of movement that are not reflective of daily use. A majority of our movements involve multiple joints and are spontaneously initiated, and an ideal evaluation should reflect these characteristics. In addition to the questionable applicability of these tests to real life, the tests require subjective calls by the evaluator. The interrater reliability between various providers administering these tests has its inherent variance and has been thoroughly described.[17,18] Together, these factors can explain why some patients report limited use despite good outcomes of clinical recovery in the ways that we have previously tested. The ActiGraph measurements address these issues by gathering objective data on patient-initiated, multijoint movements throughout various points in the patient's normal day.

It is unfair to blame clinical evaluations alone for this disconnect. The utilization of patient-reported outcomes, including patient satisfaction queries, comes with its own set of limitations. Franzblau et al[15] demonstrated that patient satisfaction after brachial plexus injury is largely varied and depends on which specific questions about satisfaction are asked and on preoperative expectations. Additionally, patients in the Franzblau et al[15] study stated that they were satisfied with their surgical outcomes and the care provided and would have surgery again; however, they were not satisfied when asked about the function of their arm. Kretschmer et al[19] demonstrated high levels of satisfaction in patients despite persistently severe levels of disability as well as the inability to resume work in their prior profession. Rasulić et al[16] demonstrated a slight disagreement between patients' improvement in quality of life and satisfaction with surgical outcome. Despite patient satisfaction being so broad, varied in its evaluation, and varied in its results, it has an ever evolving role in the health care system, including linkage to reimbursement. This further heightens the importance of understanding its evaluation.

Additional patient-reported outcome surveys have been utilized after brachial plexus repair. These range from broad evaluations like the NIH initiative PROMIS to more specific surveys aimed at nerve issues like IPAQ, DASH, DN4, SPADI, and ABILHAND. We utilized two scales to evaluate pain, DN4 and SPADI pain, which showed conflicting results. The DN4 directly correlated to both time of use and quality of use as defined by the ActiGraph. Although the DN4 had a direct correlation, the SPADI pain scale showed no relationship to movement. Multiple functional disability scales were included in this study as well: DASH, ABILHAND, SPADI disability, and IPAQ. Again, amongst the patient-reported scales focused on disability, there were differing associations with arm movement frequency and arm movement quality. The DASH and ABILHAND surveys showed clear correlations, while the SPADI disability and IPAQ surveys did not. Despite the robust nature of the PROMIS survey data, the only correlation between arm movement and subscores was fatigue, while the informational support, emotional support, anxiety, anger, and depression subscores demonstrated no relationship to arm use and quality of movement. These data and other publications showing conflicting results and interpretations with theses scales in nerve injuries support the recent advocacy for the creation of more specific brachial plexus questionnaires.[15] Similar to the surveys on satisfaction, these data demonstrate the importance of understanding the questions we ask to evaluate disability and the outcomes to which they are correlated.

Although the initial goal of this project was to test motion detectors in patients with brachial plexus repair, an interesting finding came to the forefront during data analysis. The only joint function that demonstrated a clear association with both the time of arm use and the quality of arm movement in these patients was the shoulder AROM. The patients with better shoulder function used the affected arm significantly more often and with significantly better quality. The importance of the shoulder has been recognized for many years, and was championed by Dr Gilbert; however, no data until now have been able to demonstrate the importance of shoulder function on overall arm use. These preliminary data demonstrate that the shoulder could be the limiting factor in meaningful arm use and support the importance of focusing our efforts to improve the restoration of shoulder function, especially given that adequate reanimation of the shoulder remains elusive. In areas other than brachial plexus and nerve repair, the importance of a functioning shoulder is recognized. Shoulder and rotator cuff injuries can be career ending in athletes and patients with physically demanding professions.

Although shoulder function showed the strongest correlation with arm use in this cohort, this does not devalue the importance of the restoration of elbow flexion. Brachial plexus surgery and the development of nerve transfers for elbow restoration have demonstrated huge leaps in functional outcomes. It is possible that the

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correlation with elbow flexion was not yet demonstrated due to a type 2 error and low sample size. Further studies with larger numbers will be necessary to more clearly define this relationship.

Limitations

This manuscript presents pilot data on the use of accelerometry in the evaluation of brachial plexus repair after injury. Limitations inherent to pilot data are the low number of patients included in the study and the homogeneity of the subjects (young males); however, this study neatly demonstrates the applicability of accelerometry, and the patients accurately represent the demographic that is likely to be afflicted with adult brachial plexus injuries. The third major limitation in the interpretation of results is the lack of preoperative accelerometry data. Further work will be pursued in the prospective evaluation of brachial plexus patients using accelerometry.

CONCLUSION

The current evaluation of success in brachial plexus surgery continues to be limited by clinician-elicited methods and patient recall. The use of accelerometry can overcome some of these barriers, while providing objective data on real-world use of the affected limb. Additionally, we demonstrate clearly that unless the shoulder has been reconstructed enough to place the hand in space, patients do not use the arm in real life. Therefore, the shoulder may be the limiting factor in the real-world use of the affected limb. We suggest that the shoulder joint deserves increased attention in the context of improving and advancing brachial plexus reconstruction.

Disclosures

Supported, in part, by grants from the Michigan Institute for Clinical and Health Research to Dr Lynda J.-S. Yang, and the University of Michigan MCubed Program and the Blue Cross Blue Shield of Michigan Foundation to Dr Susan H. Brown. Research reported in this publication was also supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number 2 K24-AR053120-06 to Dr Kevin C. Chung. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

This is a well-written pilot study in which the authors evaluate the use of an accelerometry-based motion detector to assess functional outcome and the real-world use of an upper extremity that has suffered an upper brachial plexus injury and underwent nerve transfers for reconstruction. Although the n is only 5, the authors present promising data that may well change the paradigm that is used to assess the outcomes of these complex nerve reconstructive strategies. The findings indicate that timely and well-performed brachial plexus reconstruction is very useful in terms of real-world functional recovery. One somewhat surprising finding is that the time of use and the magnitude of limb movement correlated with shoulder flexion and abduction, but not with other limb movements. I suspect that with a larger n, the importance of recovery of elbow flexion will also become evident statistically.

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The Impact of Intraoperative Electrocorticography on Seizure Outcome After Resection of Pediatric Brain Tumors: A Cohort Study

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Oral Presentation at the AANS/CNS Pediatric Neurosurgery Meeting, Seattle, Washington, December 11, 2015.

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Received, December 10, 2017.
Accepted, June 29, 2018.
Published Online, July 30, 2018.

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BACKGROUND: Intraoperative electrocorticography (ECoG) has been utilized in patients with tumor-associated seizures; however, its effectiveness for seizure control remains controversial.

OBJECTIVE: To evaluate clinical outcomes in pediatric patients undergoing lesionectomy with or without ECoG.

METHODS: Patients undergoing brain tumor resection at Boston Children's Hospital were examined retrospectively (2005-2014). Inclusion criteria involved diagnosis of a supratentorial tumor, ≥2 unequivocal seizures, and ≥6 mo follow-up. Patients with isolated cortical dysplasia or posterior fossa tumors were excluded. Logistic regression models evaluated predictors of ECoG use, and the impact of ECoG, gross total resection, and focal cortical dysplasia with tumors on seizure freedom by Engel Class and anti-epileptic drug use (AED).

RESULTS: A total of 119 pediatric patients were included (n = 69 males, 58%; median age, 11.3 yr). Forty-one patients (34.5%) had ECoG-guided surgery. Preoperative seizure duration and number and duration of AED use were significant predictors for undergoing ECoG. There were no differences in seizure freedom (Engel Class I) or improved Engel Score (Class I-II vs III-IV) in patients who did or did not have ECoG at 30 d, 6 mo, and 1, 2, or 5 yr. Patients undergoing ECoG required a greater number of AEDs at 6 mo ($P = .01$), although this difference disappeared at subsequent time intervals. Gross total resection predicted seizure freedom at 30 d and 6 mo postsurgery ($P = .045$).

CONCLUSION: This retrospective study, one of the largest evaluating the use of ECoG during tumor resection, suggests that ECoG does not provide improved seizure freedom compared to lesionectomy alone for children.

KEY WORDS: Electrocorticography, Engel Class, Epilepsy, Epilepsy surgery, Low grade glioma, Pediatric brain tumor, Seizure freedom

Neurosurgery 85:375–383, 2019 DOI:10.1093/neuros/nyy342 www.neurosurgery-online.com

Seizures are a common presenting sign of supratentorial pediatric brain tumors, and are observed with a frequency of approximately 38%.[1-4] Although most supratentorial pediatric brain tumors are low grade and have excellent long-term outcomes, seizure control remains a challenge for some patients. Tumor-associated seizures are more resistant to antiepileptic drugs, and the medication side-effect profile exceeds that of the traditional epilepsy population.[5-7] In tumor-associated seizures, resection is often an effective treatment, and gross total resection has proven to be a strong predictor of seizure freedom.[6,8]

Intraoperative electrocorticography (ECoG) is being increasingly utilized to increase the likelihood of achieving seizure freedom after resection by facilitating localization of epileptogenic foci adjacent to or independent from the tumor. However, the benefit of this procedure has remained controversial.[8-16] A meta-analysis in 2011 concluded that lesionectomy with

ABBREVIATIONS: AED, anti-epileptic drug; **CI,** confidence interval; **DNET,** dysembryoplastic neuroepithelial tumors; **ECoG,** intraoperative electrocorticography; **FCD,** focal cortical dysplasia; **GTR,** gross total resection; **MRI,** magnetic resonance imaging; **OR,** operating room

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intraoperative ECoG-guided tailored epilepsy surgery had no impact on patient outcomes.[12] Two recent institutional series suggest that ECoG facilitated significantly better outcomes than lesionectomy alone,[16,17] while other new reports echo no clinical improvement when ECoG is used or fail to offer a comparison group.[13,18] Thus, additional studies are needed to determine the utility of ECoG and to better inform clinical practices for pediatric patients presenting with brain tumors and concomitant seizures. In this retrospective institutional review, we sought to report our experience with seizure outcomes following tumor resection in pediatric patients with brain tumors. Our secondary aim was to evaluate the impact of ECoG on seizure control by examining pediatric patients with supratentorial tumors undergoing lesionectomy with or without intraoperative ECoG.

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METHODS

Patient Population

This was a retrospective review of a cohort of patients treated with initial surgical resection of a primary, supratentorial brain tumor and with a history of 2 or more unequivocal seizures between 2005 and 2014. Patients with tumors in the posterior fossa were excluded, as were patients greater than 18 yr of age at the time of surgery and with less than 6 mo of follow-up. Surgical resection was performed in a magnetic resonance imaging (MRI) equipped operative suite with or without ECoG. There was no set protocol for randomizing patients into surgery with or without ECoG; ECoG utilization for tumor-associated seizures was primarily conducted by 1 surgeon at the institution, and was also based on the ability to coordinate operating room (OR) booking with the neuromonitoring team, as well as the patients' and their families' or guardians' consent to the approach. The ECoG protocol is detailed below. Patients with a final pathological diagnosis of focal cortical dysplasia (FCD) without tumor were excluded.

Surgical Procedure and Completeness of Resection

All cases were performed in a MRI-OR suite. A specific, ECoG trained anesthesia and neuromonitoring team was used for all cases, even when ECoG was not used. Anesthesia worked under published protocols to obtain continuous background ECoG and maintain a stable low anesthetic depth.[19] Patients were positioned in a three-point fixation frame (Doro®, Pro Med Instruments, Breisgau, Germany) and the BrainLab system (BrainLab AG, Feldkirchen, Germany), which was used to register preoperative MR images to the stereotactic frame. Using standardized approach, ECoG was reviewed real-time by the epileptologist for signs of epileptiform activity, specifically noting areas of maximal aberrant signal (spike and wave formation, ictal recordings, and discontinuous burst suppression). Regional tissue that had abnormal signals indicative of epileptogenic foci was removed; if ECoG was positive and signals arose from eloquent cortex (determined by preoperative functional MRI and intraoperative evoked potentials), the resection was tailored to anatomy, pathology, and preoperative discussions with patients and family. After resection was completed, intraoperative MRI was performed to determine extent of resection. Residual tumor was removed, when feasible, with the goal to achieve a gross total resection. The final extent of resection was determined intraoperatively by both the operating surgeon and neuroradiologist after review of neuroimaging.

Data Collection

Data collection included patient clinical and demographic characteristics including: age at time of surgery, sex, seizure onset, frequency, and semiology, use of anti-epileptic drugs (AEDs), encephalography reports, and tumor location and pathology. Follow-up MRIs were evaluated to determine subsequent tumor progression. Postoperative seizure outcomes, graded according to Engel's classification, and the use and duration of AEDs were abstracted from clinic notes written at 1 mo, 6 mo, 1 yr, 2 yr, and 5 yr after surgery.[20] Patients were reported at each interval up until their last follow-up and all denominators are reported for each time point. This approach, as opposed to calculating a time-to-event analysis, allowed representation of a gradual decline of seizures over time, otherwise termed the "running down phenomenon."[21] Outcomes were assigned to Engel Class I, II, III, and IV, as analysis was performed in 2 ways: seizure freedom as defined by Engel Class I; and analysis of classes I and II grouped together as a satisfactory outcome, vs classes III and IV representing unsatisfactory outcome.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics in patients having surgery with or without ECoG. The impact of gross total resection and tumor associated FCD were also studied. Univariate binary and ordinal logistic regression models were used to evaluate predictors for undergoing an ECoG-guided lesionectomy, and to compare postoperative outcomes between patients with or without ECoG, gross total resection, and FCD. Two-sided *P*-values $\leq .05$ were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Human Investigation Approvals

This study was approved by and compliant with the institutional review board with a waiver of patient consent.

RESULTS

Demographic and clinical characteristics of the study cohort (n = 119) are presented in Table 1. Study subjects were primarily male (n = 69 [58%]) with a median age of 11.3 yr (range = 0.8-18.3 yr). Tumor pathology included 25 (21%) low-grade gliomas, 20 (17%) dysembryoplastic neuroepithelial tumors (DNET), 23 (19%) gangliogliomas, 19 (16%) glioneuronal tumors, and 32 (27%) other tumors, which included high-grade gliomas, meningiomas, neurocytomas, and primitive neuroectodermal tumors.

Forty-one patients (34%) underwent ECoG-guided surgery (Figure 1). As no set protocol was used to determine which patients would undergo ECoG, we evaluated demographic and clinical predictors of undergoing ECoG-guided leisonectomy using univariate logistic regression (Table 1). Preoperative seizure duration >6 mo (OR = 2.7; 95% confidence interval [CI] = 1.2-6.0; $P = .02$), increased number (overall $P = .005$) and longer duration of AED use (overall $P = .004$) were significant predictors for undergoing ECoG. ECoG use was independent of age at surgery, sex, seizure type, encephalography (EEG) findings, seizure frequency, tumor pathology, and tumor location.

Comparing outcomes between the 2 surgical approaches, no differences were seen in seizure freedom (Engel Score of I) or

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TABLE 1. Demographic and Clinical Characteristics for Patients Receiving Surgical Lesionectomy With or Without ECoG Guidance

Demographic and clinical characteristic	Total $N = 119$; (%)	No ECoG $n = 78$ (%)	ECoG $n = 41$ (%)	Odds ratio (95% CI)	*P*-value
Age at surgery (yr; median (range))	11.3 (0.8-18.3)	11.2 (0.8-18.3)	11.6 (1.5-18.1)	1 (0.9-1.1)	.79
Follow-up (mo; median (range))	53.2 (0.8-123.4)	53.6 (6-121.7)	49.2 (0.8-123.4)	–	–
Sex (Male)	69 (58)	44 (56)	25 (61)	1.2 (0.6-2.6)	.63
Preoperative seizure duration					
≤6 mo	53 (45)	41 (53)	12 (29)	Ref.	–
>6 mo	66 (55)	37 (47)	29 (71)	2.7 (1.2-6)	.017
Preoperative seizure frequency					.055[d]
Annually or less	41 (34)	31 (40)	10 (24)	Ref.	–
Monthly	26 (22)	15 (19)	11 (27)	2.3 (0.8-6.5)	.80
Weekly	40 (34)	28 (36)	12 (29)	1.3 (0.5-3.5)	.17
Daily	12 (10)	4 (5)	8 (20)	6.2 (1.5-25)	.025
Preoperative seizure type					.30[d]
Simple partial	31 (26)	21 (27)	10 (24)	Ref.	–
Complex partial	53 (45)	31 (40)	22 (54)	1.5 (0.6-3.8)	.15
Generalized/secondary generalized	35 (29)	26 (33)	9 (22)	0.7 (0.2-2.1)	.25
Preoperative EEG results					.18[d]
Normal	18/65 (28)	11/30 (37)	7/35 (20)	Ref.	–
Abnormal (site of tumor)	34/65 (52)	12/30 (40)	22/35 (63)	2.9 (0.9-9.4)	.077
Abnormal (peripheral)	13/65 (20)	7/30 (23)	6/35 (17)	1.3 (0.3-5.7)	.71
Preoperative AED Prescription (Yes)	104 (87)	65 (83)	39 (95)	3.9 (0.8-18.2)	.083
Preoperative number of AEDs					.005[d]
0	14 (12)	12 (15)	2 (5)	Ref.	–
1	83 (70)	59 (76)	24 (59)	2.4 (0.5-11.7)	.083
2	15 (13)	5 (6)	10 (24)	12 (1.9-75.7)	.055
3	7 (6)	2 (3)	5 (12)	15 (1.6-138.1)	.078
Preoperative AED duration					.004[d]
<1 mo	51 (43)	42 (54)	9 (22)	Ref.	–
1 to 6 mo	31 (26)	18 (23)	13 (32)	3.4 (1.2-9.3)	.34
>6 mo	37 (31)	18 (23)	19 (46)	4.9 (1.9-12.9)	.018
Tumor location					
Temporal	60 (50)	40 (51)	20 (49)	Ref.	–
Nontemporal	59 (50)	38 (49)	21 (51)	1.1 (0.5-2.4)	.80
Pathology					
Low grade glioma	25 (21)	13 (17)	12 (29)	Ref.[a]	–
Dysembryoplastic neuroepithelial	20 (17)	11 (14)	9 (22)	0.9 (0.4-2.2)[b]	.90
Ganglioglioma	23 (19)	15 (19)	8 (20)		
Glioneuronal tumor	19 (16)	11 (14)	8 (20)		
Other[c]	32 (27)	28 (36)	4 (10)		
WHO grade					
Low (1-2)	105/118 (89)	66 (85)	39/40 (98)	Ref.	–
High (3-4)	13/118 (11)	12 (15)	1/40 (3)	0.1 (0-1.1)	.07
Focal cortical dysplasia					
Absent	98 (82)	67 (86)	31 (76)	Ref.	
Present	21 (18)	11 (14)	10 (24)	2 (0.8-5.1)	.17

Abbreviations: AED: antiepileptic drugs; ECoG: electrocorticography; EEG: electroencephalography; NA: not applicable.

[a]In the logistic regression analysis, low grade glioma and dysembryoplastic neuroepithelial tumor were combined in one group (reference), the comparison group included gangli-oglioma, glioneuronal tumor, and other pathology.

[b]Odds ratio for a combined group of ganglioglioma, glioneuronal, and other pathology vs reference group (low-grade glioma and dysembryoplastic neuroepithelial tumor combined).

[c]Other pathology includes high grade glioma, meningioma, neurocytoma, and primitive neuroectodermal tumor.

[d]Global *P*-values are presented for variables that have more than 2 categories, obtained using type 3 analysis, a global *P*-value determines the significance of a variable overall, not of a specific category.

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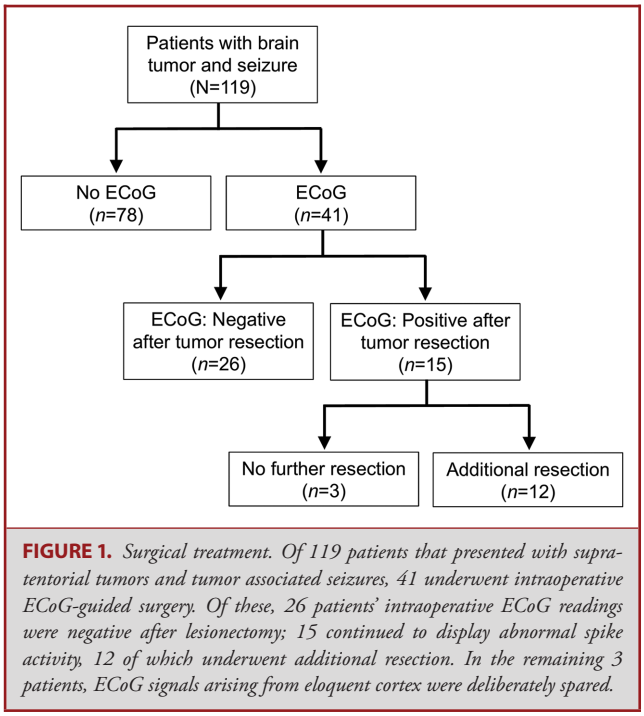


FIGURE 1. *Surgical treatment. Of 119 patients that presented with supratentorial tumors and tumor associated seizures, 41 underwent intraoperative ECoG-guided surgery. Of these, 26 patients' intraoperative ECoG readings were negative after lesionectomy; 15 continued to display abnormal spike activity, 12 of which underwent additional resection. In the remaining 3 patients, ECoG signals arising from eloquent cortex were deliberately spared.*

Engel Score (Class I and II vs III and IV) at 30 d, 6 mo, 1 yr, 2 yr, or 5 yr (Table 2). Operative complications were grossly the same for the ECoG and non-ECoG groups. Of note, >80% of patients with and without the use of ECoG had Engel Class I or Class II outcomes at all-time points (Figure 2A). ECoG patients were taking a greater number of AEDs at 6 mo ($P = .01$), but this difference disappeared at subsequent time intervals (Table 2, Figure 2B).

Of the 41 individuals undergoing ECoG, 26 (63.4%) patients' intraoperative ECoG readings were negative after the tumor resection (Figure 1); 15 (36.6%) continued to display spike and waveform abnormalities on ECoG after the initial tumor resection (Table 3 and 4). Twelve of these patients underwent additional resection. In the remaining 3 patients, ECoG signals were arising from eloquent cortex (determined by preoperative functional MRI and intraoperative evoked potentials), and decision to deliberately spare those areas and accept near-total resection was based upon anatomy, pathology, and preoperative discussions with patients and family. Of those 3 patients, 1 remained seizure free for the 5-yr duration of follow-up, whereas 2 had a seizure in the perioperative period, but then remained seizure free for the 1-yr and 2-yr durations of follow-up, respectively. Of the 12 who underwent additional, tailored resection, 8 were classified as Engel I, 1 as Engel II, 2 as Engel III, and 1 as Engel IV at their last follow-up appointment.

During examination of other predictors of seizure outcome, gross total resection significantly predicted seizure freedom at 30 d and 6 mo postsurgery (Table 5; $P = .045$), however, the effect was not sustained beyond 6 mo (near significance at 2 and 5 yr with $P = .06$ and $P = .08$, respectively). FCD had no effect on seizure freedom or AED use (**Table**, **Supplemental Digital Content**). Tumor location (temporal vs nontemporal) and pathology (low-grade glioma and dysembryoplastic neuroepithelial vs gangli-oglioma, glioneuronal, and other) did not associate with seizure freedom or AED use (data not shown).

TABLE 2. Comparison of Postoperative Seizure Outcomes. The Odds Ratios Below Demonstrate the Odds of an Outcome After ECoG Compared to Odds of an Outcome With Lesionectomy Alone

Postoperative seizure outcome	n	Odds ratio (95% CI)	*P*-value
Seizure freedom at 30 d	119	1.7 (0.7-3.8)	.21
Seizure freedom at 6 mo[a]	116	0.9 (0.4-2.4)	.90
Seizure freedom at 1 yr	116	0.8 (0.3-2)	.65
Seizure freedom at 2 yr	97	0.9 (0.3-2.7)	.92
Seizure freedom at 5 yr	50	0.8 (0.2-3.2)	.73
Binary Engel Score (Class I + II vs III + IV)			
Engel score 6 mo	116	1.6 (0.3-8.1)	.60
Engel score 1 yr	116	0.8 (0.2-2.9)	.70
Engel score 2 yr	97	1 (0.2-4.4)	.96
Engel score 5 yr	50	1.2 (0.2-7)	.83
AED use[b]			
Number of AEDs 6 mo (lower)	117	0.4 (0.2-0.8)	.013
Number of AEDs 1 yr (lower)	116	0.7 (0.3-1.4)	.26
Number of AEDs 2 yr (lower)	97	0.8 (0.3-1.7)	.53
Number of AEDs 5 yr (lower)	50	0.7 (0.2-2.2)	.49
Duration of AED use (shorter)[c]	111	0.7 (0.3-1.4)	.26

Abbreviations: AED: antiepileptic drugs; ECoG: electrocorticography.
[a]Seizure freedom is defined as Engel score of 1.
[b]Anti-epileptic drug (AED) use is an ordinal outcome, number of AEDs ranges from 0 to 4, probability is modeled over the lower values.
[c]Duration of anti-epileptic drug (AED) use is an ordinal outcome that includes 4 categories: <6 mo, 6 mo to 1 yr, 1 to 2 yr, and >2 yr, probability is modeled over the shorter durations.

DISCUSSION

A subset of patients with brain tumors experience tumor-associated seizures and the efficacy of electrocorticography (ECoG) as a tool to facilitate surgery for these individuals remains unclear. The majority of evidence for ECoG in patients with brain tumors is from retrospective, single institution data, so a meta-analysis was performed in 2011 by Englot et al[12] to collate 20 published studies on 773 patients with tumor related seizures (100 patients undergoing ECoG). The authors concluded that ECoG offered no significant benefit over lesionectomy alone. Since then, subsequent single-institution studies have been reported and the long-term benefit of ECoG remains to be convincingly established.[13,16,17] Our study was intended to add to the current body of literature, particularly that of pediatric patients, with hopes to further elucidate the impact of ECoG in resective surgery.

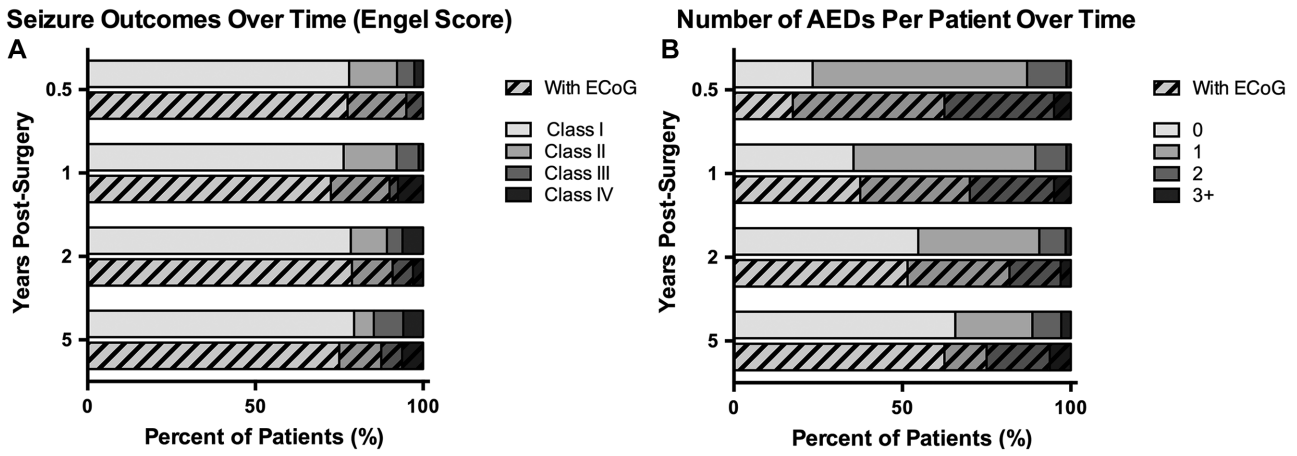


FIGURE 2. *Postoperative seizure outcomes. Outcomes were compared between patients undergoing lesionectomy alone vs lesionectomy plus electrocorticography-guided surgery (diagonally striped bars).* **A**, *When comparing Engel Class I and II to Classes III, and IV at 6 mo, 1, 2, and 5 yr postsurgery, no differences were seen in seizure freedom or control.* **B**, *Examining the use of AEDs per patient, up to 5 yr after surgery, there was no significant association between ECoG and the number of postoperative AEDs. Abbreviations: AEDs, antiepileptic drugs; ECoG, electrocorticography.*

TABLE 3. Demographics for Patients who had a Positive Electrocorticography (ECoG) Reading After Tumor Resection

Patient	Age	Year of surgery	Tumor location	Tumor pathology	Seizure duration (mo)	Seizure type	Preoperative seizure frequency	Pre-operative duration of AED use (mo.)	Number of AEDs taking	Gross total resection of tumor	Had additional resection when positive ECoG
1	2	2009	Left temporal	LGG	>6	Complex partial	Daily	14	2	Yes	Yes
2	6	2007	Right temporal	DNET	≤6	Complex partial	Weekly	2	1	Yes	Yes
3	7	2008	Left temporal	Ganglioglioma	>6	Simple partial	Weekly	1	1	No	Yes
4	8	2011	Right temporal	LGG	>6	Simple partial	Annually or less	0	0	Yes	Yes
5	10	2008	Left temporal	Glioneuronal	>6	Complex partial	Weekly	3	1	Yes	Yes
6	11	2012	Right parietal	DNET	>6	Generalized[a]	Monthly	13	2	No	Yes
7	12	2013	Left temporal	Ganglioglioma	>6	Complex partial	Monthly	72	2	Yes	Yes
8	13	2011	Left temporal	Ganglioglioma	>6	Complex partial	Daily	5	1	Yes	Yes
9	13	2013	Right temporal	DNET	≤6	Complex partial	Annually or less	2	1	Yes	Yes
10	14	2005	Right temporal	Ganglioglioma	>6	Complex partial	Weekly	12	2	Yes	Yes
11	16	2010	Left frontal	DNET	≤6	Simple partial	Monthly	1	1	Yes	Yes
12	18	2011	Left temporal	LGG	>6	Complex partial	Daily	36	3	No	Yes
13	6	2005	Right temporal	LGG	>6	Generalized[a]	Annually or less	6	3	Yes	No
14	16	2013	Right frontal	LGG	>6	Complex partial	Weekly	24	2	Yes	No
15	17	2010	Right temporal	HGG	>6	Complex partial	Daily	72	2	Yes	No

Abbreviations: AED: antiepileptic drug; DNET: dysembryoplastic neuroepithelial tumor; ECoG: electrocorticography; HGG, high grade glioma, LGG: low grade glioma; mo: months.
[a]Generalized includes secondary generalization.

This single center, consecutive series of children undergoing surgery for tumor related seizures is one of the largest pediatric cohorts reported. It suggests that tumor resection with ECoG does not improve likelihood of seizure freedom. There was no difference in Engel Class outcomes between the groups. Notably, Engel Class I outcomes were achieved in nearly 80% of cases in both groups. Looking at acceptable seizure control of either Class I or II, >80% of patients in both groups achieved such outcomes at all-time points, suggesting that tumor resection alone was likely sufficient. Another philosophy behind ECoG use is to identify secondary cortical changes that may have arisen at a greater distance from the tumor. Recent literature suggests that

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TABLE 4. Postoperative Details for Patients who had a Positive Electrocorticography (ECoG) Reading After Tumor Resection

Patient	ES 6 mo	AED # 6 mo	ES 1 yr	AED # 1 yr	ES 2 yr	AED # 2 yr	ES 5 yr	AED # 5 yr	Follow-up (mo)	Last recorded ES	Postoperative symptoms
1	0	2	0	1	0	1	0	0	88	0	N/A
2	0	1	0	1	0	1	1	0	102	1	Severe behavioral and attentional regulation issues (eg stealing, impulsivity)
3	0	1	0	0	0	0	0	0	70	0	Difficulty with fine motor movements; unable to perform pincer grasp. Some sensory loss in lower extremities
4	0	0	0	0	0	0	.	.	39	0	Change in farsightedness in left eye
5	0	1	1	1	0	1	0	1	79	0	Slightly brisk reflexes and some tumor recurrence
6	0	2	0	2	0	1	.	.	32	0	N/A
7	0	1	.	.	.	.	.	.	6	0	Learning disability
8	1	2	3	2	3	3	.	.	37	3	Occasional seizures. No neurological deficits
9	1	1	1	0	2	1	.	.	22	2	Fatigue
10	0	2	0	2	1	2	0	2	65	0	N/A
11	0	1	0	1	0	0	.	.	55	0	Thoracic outlet syndrome
12	1	2	1	2	1	2	2	2	33	2	N/A
13	0	4	0	4	0	1	0	1	125	0	Impairment in expressive and receptive vocabulary
14	0	2	0	2	.	.	.	.	19	0	N/A
15	0	2	0	2	0	2	.	.	55	0	N/A

Abbreviations: AED: antiepileptic drug; DNET: dysembryoplastic neuroepithelial tumor; ECoG: electrocorticography; ES: Engel Score; HGG, high grade glioma, LGG: low grade glioma; mo: months.
The dotted horizontal line above patient 13 separates those who had a positive ECoG reading after tumor resection who did or did not undergo additional tissue resection.

TABLE 5. Association Analysis of Postoperative Outcomes for Subtotal vs Gross Total Resection

Postoperative seizure outcome	n	Odds ratio (95% CI)	*P*-value
Seizure freedom at 30 d[a]	119	0.4 (0.2-1)	.044
Seizure freedom at 6 mo	116	0.4 (0.2-1)	.045
Seizure freedom at 1 yr	116	0.6 (0.3-1.6)	.34
Seizure freedom at 2 yr	97	0.4 (0.1-1)	.06
Seizure freedom at 5 yr	50	0.3 (0.1-1.2)	.08
Engel Score Class I + II (vs III + IV)			
Engel score 6 mo	116	0.6 (0.1-2.6)	.48
Engel score 1 yr	116	0.9 (0.2-3.6)	.86
Engel score 2 yr	97	0.6 (0.1-2.2)	.40
Engel score 5 yr	50	0.2 (0-1.2)	.09

[a]Seizure freedom is defined as Engel score of I.
Odds ratios demonstrate the odds of an outcome after near-subtotal resection compared to odds of an outcome with gross total resection. Gross total resection showed decreased odds of seizure presence after 30 d of surgery, and at 6 mo ($P \leq .045$).

changes in the tumor microenvironment may lead to formation of secondary epileptogenic foci.[22-24] For this reason, we examined cases with FCD on pathology, but found no significant patterns with tumor-associated FCD and clinical outcome.

Irrespective of ECoG utilization, many studies argue that the most significant predictor of seizure freedom in these patients is gross total resection (GTR).[12,25-30] Our series corroborated such findings, as GTR was a significant predictor of seizure freedom at 30 d and 6 mo postsurgery (with a trend nearing significance at 2 and 5 yr). Importantly, the likelihood of achieving GTR is improved with intraoperative MRI,[31,32] and at Boston Children's Hospital, we routinely use intraoperative MRI to increase the extent of tumor resection. It may be that hospitals equipped with robust MRI operating rooms reliably achieve maximum safe resections; in these cases, ECoG may have marginal added benefit. However, in hospitals lacking intraoperative MRI or an MRI in general–such as in low resource settings–it is possible that ECoG may help distinguish tumor from healthy parenchyma, facilitate GTR, and confer additional clinical benefits. Unfortunately, the impact of ECoG on GTR in the absence of intraoperative MRI cannot be readily discerned given the lack of data disaggregation in the literature.[10,12,13,16,17,33]

Our conclusions parallel the most recent 2011 meta-analysis of seizure freedom after resection of supratentorial low-grade gliomas,[12-14] as well as many other recent publications,[10,22] but lie in contrast to studies suggesting that ECoG guided resection may result in a greater likelihood of long-term seizure freedom.[16,17] First, we would like to address those advocating for ECoG. The recent pediatric study by Fallah et al[16] used ECoG almost routinely, so while their results support ECoG use, they admit their inability to draw conclusions on the added utility, if any, of an ECoG tailored resection compared with a lesionectomy-only approach. In their comparison of 55

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lesionectomy only and 29 ECoG-tailored resections, there was no statistically significant difference in patient outcome, though GTR exhibited a trend toward association with seizure freedom. In another cohort described by Qui et al, 87.5% of patients (n = 32) who underwent ECoG guided tailed epilepsy surgery achieved an Engel I score outcome compared to 63.8% of controls (n = 103). Their patients' ages ranged from 5 to 66 with an average age of 37 yr. While the authors did not stratify result by age, they note in their discussion that lesionectomy alone may be sufficient for pediatric patients, whereas adults may benefit more from ECoG. Additionally, neither of these studies supporting ECoG utilized intraoperative MRI to assure GTR, but both alluded to the importance of complete resection in seizure freedom.

In contrast, many studies support the notion that lesionectomy may be sufficient for these pediatric patients.[13-15,18,34] Bansal et al[18] published a subanalysis of pediatric patients with tumor associated epilepsy and showed no correlation between ECoG features and improved outcomes. Kim et al[34] showed analogous results, but stressed that GTR was a better predictor of seizure freedom. In 52 pediatric patients, Wray et al[14] reported that the presence or absence of epileptiform discharges on post-ECoG was not predictive of seizure freedom. In their series, 37 individuals had postresection ECoG discharges, yet 73% were seizure-free after surgery. In contrast, 15 of their patients had zero epileptiform discharges on postresection ECoG, yet 40% of those patients suffered from sustained seizures. In our study, the 3 patients with residual discharges following resection remained seizure free (excluding the perioperative period), whereas 33% of the patients who underwent additional resection for epileptiform discharges on post-resection ECoG had Engel Class greater than I. Fang et al[15] note that ECoG changes before and after resection have predictive value for early postoperative seizures within 1 wk from surgery, but not thereafter. Overall, the utility of ECoG readings during tumor resection, particularly for pediatric patients, remains uncertain.

These conflicting results are likely multifactorial, reflecting differences in patient pathology and stage of disease, institutional variation in experience and volume, ECoG and surgical protocols, and other unknown confounders. While our data suggests that pediatric patients with tumor associated seizures are unlikely to glean additional benefit from an ECoG-guided resection, additional research is needed to determine if patient subgroups would benefit from ECoG. A randomized, prospective study will be needed to elucidate the efficacy of ECoG-tailored surgery for tumor associated seizures.

Limitations

The limitations of both the ECoG technique and this study warrant further discussion. When using ECoG, it is uncommon to record intraoperative ictal activity, so resection margins are frequently determined using interictal data.[35] Furthermore, as demonstrated by Fang et al[14] in 2012, the predictive value of postresection ECoG on clinical outcome is uncertain. Additional tissue resection may put the patient at risk for further neurological deficits,[36-38] without certain benefit in seizure outcome.[14] Finally, ECoG increases cost, personnel, and duration of the procedure, and no detailed cost-effectiveness analysis has been performed.

The generalizability of this study should be carefully considered. While these data comprise one of the largest groups of patients in the pediatric brain tumor population, it is a single institution study. The participating surgeons operate at large case volumes and routinely achieve gross total resection with the help of intraoperative MRI. Consequently, a high percentage of their patients achieve Engel I status with lesionectomy alone, which may obscure the ability to see incremental benefit from ECoG. However, it is plausible that institutions with lower patient volumes or without an intraoperative MRI might see improved seizure outcome with the addition of ECoG, if it aids in achieving a more complete resection of the tumor and epileptogenic tissue.[4,12] Additionally, as this was not a randomized, controlled trial, there may have been an inherent bias in the use of ECoG in particular patients. ECoG appeared to have been used in more severe cases of seizure pathophysiology (more frequent seizures over a longer duration), and with lesions less amenable to gross-total resection secondary to involvement of eloquent cortex.

CONCLUSION

In this retrospective institutional study of pediatric patients with tumor associated seizures, the use of ECoG compared to lesionectomy alone for supratentorial brain tumor resection did not result in a significant difference in seizure freedom or a reduction in the number of AEDs used postoperatively. As gross total resection was the most significant predictor of seizure freedom in the first 6 mo after surgery, the most important consideration may be to ensure that an institution has a method of either radiological or electrographic intraoperative assessment to facilitate complete resection. Importantly, as our results are consistent with the latest systematic review but lie in contrast with recent institutional publications, we hope to emphasize that a more robust study is needed to reach consensus. A prospective clinical trial with randomization to surgery with or without ECoG could address potential treatment selection bias and more definitively evaluate the merits of ECoG-guided lesionectomy.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Table. Associations between FCD and postoperative outcomes. The odds ratios below demonstrate the odds of an outcome for 21 patients with FCD on the surgical pathology report compared to the 98 patients without FCD.

COMMENTS

The authors have evaluated the role of intraoperative electrocorticography in the management of refractory epilepsy in a large cohort of children a variety of brain tumors. The authors used an intraoperative MRI to ensure complete resection of the "tumor". In 41 patients, intraoperative electrocorticography was performed and if persistent ECoG abnormalities noted, further resection performed if possible, and additional resection done and completeness of resection confirmed with an intraoperative MRI. All patients were operated in the iMRI and completeness of resection confirmed unless limited by eloquent cortex.

Hence, the authors did not really have a group of patients in whom *only* ECoG-guided resection done except when resection was close to eloquent cortex. It would be fair to state that for centers where an Intraoperative MRI is not available, intraoperative electrocorticography can help maximize the seizure outcome.

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The authors of this important paper investigating the role of ECoG in epilepsy associated brain tumor surgery are to be congratulated on their excellent outcomes. This manuscript is a retrospective report of the outcome of 119 pediatric patients (median age 11.3 years) with supratentorial brain tumors and at least 2 seizures. The author's aims were to report seizure outcome and also to evaluate the impact of intraoperative ECoG. Forty-one of the 119 underwent ECoG. All surgery was performed with availability of intraoperative MRI (iMRI). The authors found no difference in outcome, with more than 80% of all patients (both the ECoG and non-ECoG groups) were either Engel 1 or 2 at follow-up. Gross total resection (GTR) was the most important factor they report. Interestingly, 15/41 ECoG patients had positive ECoG findings, with 12/15 having further resection based on ECoG findings in the OR, with 9/12 Engel 1/2, and 3/15 did not have further resection because of proximity to eloquent cortex, but all of whom are seizure free at follow-up. This impressive series supports the impression that lesionectomy alone is sufficient in these cases, and that intraoperative ECoG does not change the outcome.

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The study's authors compared the effect of electrocorticography guided tumor resection vs lesionectomy alone on seizure outcome in children. This was a retrospective, single-institution, longitudinal cohort analysis comparing seizure-related outcome variables that include seizure freedom, Engel score, and number of anti-epileptic medications at 30 days and up to 5 years.

The results of the study indicate no difference across these variables and corroborate prior data that extent of resection is the most significant predictor of good seizure control. However, the decision to employ ECoG was not protocolized and consisted of preoperative characterization of seizure-related clinical variables. As such, it is felt that this bespeaks an inherent selection bias to the methodology.

Nevertheless, this work directs us to ask relevant questions such as the utility of positive ECoG findings in short- versus long-term follow-up, as well as the correlation between certain intraoperative electrographic elements and pathology, seizure network profile, and margins.

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Predicting Inpatient Length of Stay After Brain Tumor Surgery: Developing Machine Learning Ensembles to Improve Predictive Performance

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Received, January 22, 2018.
Accepted, June 30, 2018.
Published Online, August 3, 2018.

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BACKGROUND: Current outcomes prediction tools are largely based on and limited by regression methods. Utilization of machine learning (ML) methods that can handle multiple diverse inputs could strengthen predictive abilities and improve patient outcomes. Inpatient length of stay (LOS) is one such outcome that serves as a surrogate for patient disease severity and resource utilization.
OBJECTIVE: To develop a novel method to systematically rank, select, and combine ML algorithms to build a model that predicts LOS following craniotomy for brain tumor.
METHODS: A training dataset of 41 222 patients who underwent craniotomy for brain tumor was created from the National Inpatient Sample. Twenty-nine ML algorithms were trained on 26 preoperative variables to predict LOS. Trained algorithms were ranked by calculating the root mean square logarithmic error (RMSLE) and top performing algorithms combined to form an ensemble. The ensemble was externally validated using a dataset of 4592 patients from the National Surgical Quality Improvement Program. Additional analyses identified variables that most strongly influence the ensemble model predictions.
RESULTS: The ensemble model predicted LOS with RMSLE of .555 (95% confidence interval, .553-.557) on internal validation and .631 on external validation. Nonelective surgery, preoperative pneumonia, sodium abnormality, or weight loss, and non-White race were the strongest predictors of increased LOS.
CONCLUSION: An ML ensemble model predicts LOS with good performance on internal and external validation, and yields clinical insights that may potentially improve patient outcomes. This systematic ML method can be applied to a broad range of clinical problems to improve patient care.

KEY WORDS: Length of stay, Machine learning, Outcomes, Predictive modeling

Neurosurgery 85:384–393, 2019 DOI:10.1093/neuros/nyy343 www.neurosurgery-online.com

Machine learning (ML) is a powerful analytic tool that uses computer algorithms to recognize patterns in data that are not explicitly programmed.[1] Historically, regression-based algorithms have dominated predictive modeling in medicine.[2] These algorithms assume certain relationships between variable coefficients and outcomes and that variables function independently to influence outcomes. Given the complexity of human disease, these assumptions may not hold. Increasing emphasis is being placed on the potential of nonregression ML algorithms to improve outcomes research.[3-4] Many of these algorithms can handle and combine vast numbers of variables in complex and nonlinear ways to generate sophisticated predictions.[4] Predictive models based on these techniques may therefore help providers identify clinically significant risk in patients whose constellation of risk factors may otherwise have been missed, or identify novel and unexpected predictors of risk.[5-7] Although used extensively in medical

ABBREVIATIONS: CI, confidence intervals; **LOS,** length of stay; **ML,** machine learning; **NIS,** National Inpatient Sample; **NSQIP,** National Surgical Quality Improvement Program; **RMSLE,** root mean square logarithmic error

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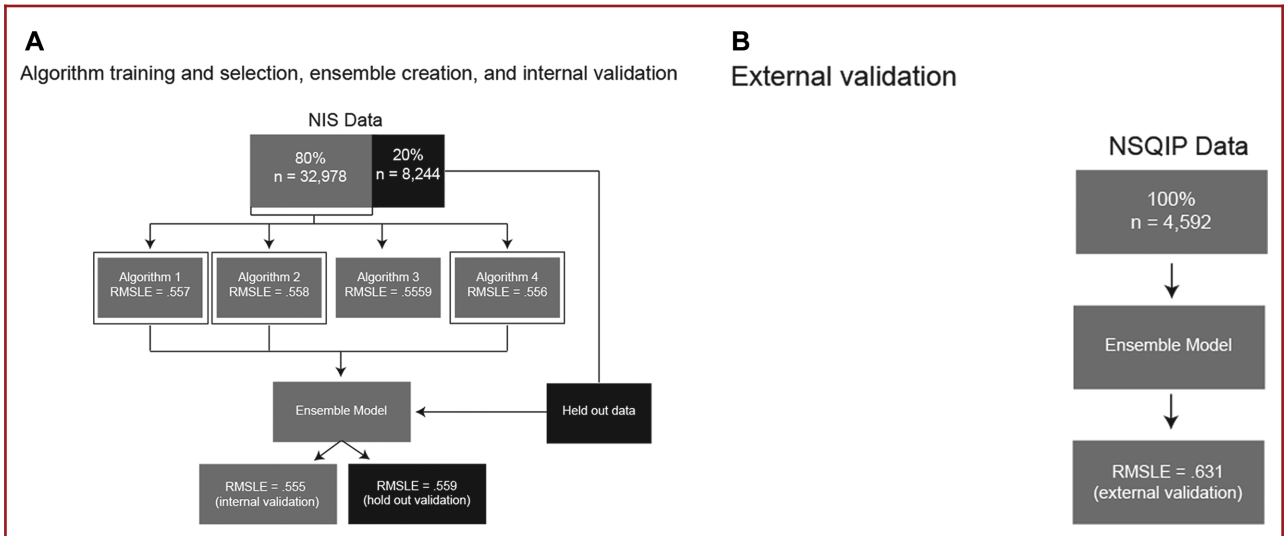


FIGURE 1. *Methods overview.* **A**, *Description of algorithm training and validation (using RMSLE as validation metric), selection of the top three performing algorithms (the three algorithms with validation RMSLE closest to 0), combination of these algorithms into a separate, ensemble model, and internal and holdout validation.* **B**, *External validation of the ensemble model using an entirely separate database derived from the NSQIP. RMSLE, root mean square logarithmic error; NIS, National Inpatient Sample; NSQIP, National Surgical Quality Improvement Project.*

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imaging and genomics, the use of nonregression ML algorithms to model clinical outcomes is less well-established.[8-12]

Nonregression ML has been used in clinical medicine, including predicting survival in glioma patients following surgery using support vector machines[13] and diagnosing diabetic retinopathy from retinal fundus photographs using neural networks.[14] A variety of ML techniques have been described. Often a particular ML algorithm is selected a priori and thus may not necessarily arrive at the optimal solution. Although certain ML algorithms have theoretical advantages over others, the only way to know with certainty which algorithm will produce the best predictions is by direct comparison of the predictive power of different algorithms.

Here, we propose a unique technique for predicting patient outcomes that leverages the power of many types of ML: to guide algorithm selection, we evaluate and rank the predictive abilities of a broad range of ML algorithms before combining the best performers into an ensemble, allowing us to take advantage of the complementary strengths of multiple algorithms.[15] In this proof-of-concept study, we build and internally validate a guided ML ensemble to predict length of stay (LOS)in hospital of patients following craniotomy for brain tumor from preoperative patient variables recorded in the National Inpatient Sample (NIS). We then externally validate the ensemble using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. Finally, we use permutation importance analyses and partial dependence plots to understand the independent impact of variables that the ensemble deems important in order to glean clinical insights (Figure 1).

We chose to model LOS in part because it has been identified as a primary driver of increasing cost for craniotomy for brain tumor.[16] Accurate modeling of this outcome can help providers identify risk factors for, and potentially cut down on, unnecessary hospital days after craniotomy for brain tumor, decreasing waste and potentially improving care for these patients.

METHODS

Training Database

We used the NIS database from 2002 to 2011 to train and internally validate the ensemble. The NIS is the largest publicly available all-payer inpatient database in the United States, representing roughly 8 million hospital stays from ~1000 hospitals. The database is built to approximate a 20% stratified sample of nonfederal US hospitals (The Agency for Healthcare Research and Quality, Rockville, Maryland).[17]

External Validation Database

For external validation, we used data from the NSQIP from 2012 to 2013. The NSQIP, which is administered by the American College of Surgeons, is a multi-institutional program that prospectively collects data on randomly selected surgical patients from over 400 academic and private hospitals across the United States.[18] We selected years outside of the range included in the training database to ensure no overlap between the training and validation databases.

Both the NIS and NSQIP are publicly available, deidentified databases, and were considered exempt from Institutional Review Board review.

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Patient Selection

We screened each of 79 742 743 admissions registered in the NIS from 2002 to 2011 for inclusion in the training dataset, and each of 1195 375 admissions registered in the NSQIP between 2012 and 2013 for inclusion in the external validation dataset. Eligible admissions were identified by International Classification of Diseases (ICD)9 diagnosis codes for brain tumor (225.0-225.4, 225.8, 225.9, 199.1, and 191.0-191.9) and ICD9 procedure codes matching craniotomy in the NIS dataset (01.20-01.29, 01.31, 01.32, 01.39, and 01.59), or Current Procedural Terminology (CPT) codes for craniotomy in the NSQIP dataset (61 510, 61 512, 61 518-61 521, 61 526, and61 530). Only patients 18 yr or older were included. In total, 41 222 admissions met criteria for inclusion in the training dataset, and 4592 admissions met criteria for inclusion in the external validation dataset.

Variable Selection and Primary Outcomes

A variety of preoperative patient characteristics were collected that are available in both the NIS training and the NSQIP validation datasets, including age, race, sex, specific neurosurgical diagnosis, preoperative comorbidities, admission quarter (within the year of hospitalization), and emergent vs nonemergent surgery. In total, 26 different variables were considered (see Table, **Supplemental Digital Content 1** for listed variables).

Data Preprocessing

Missing numerical data were imputed using the median value for the given variable, and a new binary variable created to denote the imputation.[19,20] Some algorithms (decision tree-based models in particular) are well suited to detect and leverage variable interactions in ways that linear models are not, while at the same time being unable to function (algorithmically) in the presence of missing data. Using this approach to handling missing data allows the greatest number of algorithms to train while still permitting those that can leverage imputation to do so.

Each column of numeric data was standardized by subtracting the mean value of the column and then dividing by its standard deviation. For linear algorithms, one-hot encoding was used to transform categorical data into multiple binary columns. Missing categorical values were treated as their own category and got their own column. For tree-based algorithms, categorical data was encoded using randomly assigned integers.

Algorithm Selection and Ensemble Validation

Prior to training, 20% of the training dataset was randomly selected as the holdout and excluded from training.[19,20] The remaining data was divided into 5 mutually exclusive folds, For each of 29 algorithms training was performed 5 times, with each fold used once for validation and the remaining 4 used together as training.[21] In choosing a 5-fold (as opposed to a higher fold) validation, we made a tradeoff between algorithm training run time and additional estimates of ensemble generalizability on cross-validation. To offset this tradeoff, we evaluated the final model against an entirely separate database, the NSQIP, which is the ultimate measure of the ensemble's ability to generalize to new data.

Model hyperparameters were optimized within each fold by creating an additional sub-fold training/validation split. Each combination of hyperparameters was tested within this sub-fold training/validation setup to determine optimal hyperparameters. The algorithm was then retrained using these hyperparameters.

We calculated cross-validation scores by taking the root mean square logarithmic error (RMSLE) of the 5 possible validation folds (the closer to 0 the RMSLE value, the more accurate the model, with a RMSLE = 0 denoting zero error). We chose RMSLE as our validation metric because it penalizes large error less when both predicted and actual LOS are very large than when predicted and actual LOS are small. RMSLE can be interpreted as the standard deviation of the log of unexplained variance (eg, error). A less-than-technical treatment would be: "the model's prediction is usually within e to the power of the calculated RMSE times the true value." The algorithms with the highest cross-validation scores were identified and combined with an elastic net to form an ensemble.

The ensemble model was trained and cross-validated in the same manner as the individual algorithms. As additional internal validation, the RMSLE was calculated for predictions made on the never-before-seen holdout dataset. Following internal validation, the ensemble was trained on 100% of the NIS database. The fully trained model was then externally validated with the NSQIP database (Figure 1). The NIS holdout and the NSQIP dataset were taken to be one sample of data with a single RMSLE and so no confidence intervals (CI) were calculated. ML software from DataRobot, Inc was used for model training and validation (DataRobot ver 3.0, Boston, Massachusetts).

We generated lift charts in order to visualize how accurately each ensemble model predicts LOS. To generate these charts, we ranked and divided the ensemble predictions into 10 "bins" and calculated the average predicted LOS for each bin. We then calculated the average actual LOS for each decile and plotted the average predicted values against the average actual values.

Permutation Importance

We used permutation importance to compute the relative importance of a variable to the final ensemble.[19,20,22] The ensemble was retrained on a version of the data in which all values for the variable in question are randomly permuted, which removes any predictive value of the variable while maintaining its distribution. We then compared the difference in RMSLE between the original model and the model built with the permuted variable. By calculating the change in model performance for each permuted variable, we can rank the relative importance of each variable to the model, with more important variables yielding greater losses in model performance.

Partial Dependence

Partial dependence plots allow one to visualize how a model reacts to changes in a single variable.[19,20,23] To generate these plots, a random subset of the training data is selected. For each variable, all the values for the variable are replaced with one of many constant test values. Predictions are made using the test values and the mean value of the predictions calculated. The mean prediction is plotted over the test values to generate a visual representation of the model's response to changes in the variable. For categorical variables, we tested each value seen in the training data. For numerical values, we tested values over regularly spaced intervals between the maximum and the minimum observed value.

Other Statistical Methods

Additional statistical analysis was performed to describe selected patient and hospital characteristics. We compared continuous variables using the Mann–Whitney *U* test and categorical variables using Pearson's

χ^2 test. All analyses were performed with open source tools available from SciPy (SciPy ver 0.17, http://www.scipy.org/).

RESULTS

Patient Characteristics

A total of 41 222 admissions for craniotomy for brain tumor were reviewed for analysis. Average LOS was 7.8 d (standard deviation = 8.7 d). One admission was excluded from the study because it had no recorded LOS. Patients who are male ($P = .02$), non-White ($P < .001$), have nonelective surgery ($P < .001$), and have comorbidities ($P < .001$) tend to have longer hospitalizations (Table 1). The NIS and NSQIP patient populations differed significantly from each other in a variety of ways (**Table**, **Supplemental Digital Content 2**).

Algorithm Leaderboard

Twenty-nine ML algorithms, including tree-based models, linear classifiers, support vector machines, RuleFit, neural networks, and naïve Bayes classifiers, were trained to predict the primary outcomes. The top performing algorithms were 2 gradient boosted trees and a Nystroem kernel support vector machine. These were combined with an elastic net to create an ensemble model.

RMSLE and Lift Chart for the Ensemble Model

The ensemble model had a RMSLE of .555 (95% CI, 0.553-0.557) on internal validation, a RMSLE of 0.559 for the holdout, and a RMSLE of 0.631 on external validation. Lift charts for both the internal and external validation are shown below (Figure 2, Table 2).

Permutation Importance and Partial Dependence

The variables that most strongly influence LOS are as follows: nonelective craniotomy, preoperative pneumonia, preoperative sodium abnormality, preoperative weight loss, and non-White race (Figure 3). Nonelective surgery independently increased predicted LOS from 6.3 to 9.7 d; pneumonia (defined as new or recently diagnosed) independently increased predicted LOS from 7.6 to 20.4 d; preoperative sodium abnormality independently increased predicted LOS from 7.4 to 12.1 d; and preoperative weight loss (defined as > 10% decrease in body weight in the 6 mo prior to surgery) independently increased predicted LOS from 7.5 to 16.1 d. Identifying as African American (9.6 d), Hispanic (9.1 d), Asian (8.8 d), American Indian or Alaska Native (9.1 d) conferred a longer LOS than identification as White (7.4 d; Figure 4). Patients with multiple risk factors had higher predicted LOS, though risk was not necessarily additive; for example, an African American patient with pneumonia and a nonelective surgery was predicted to have a LOS of 24 d (actual LOS = 30 d).

TABLE 1. Characteristics of Patients Used for Algorithm Training

Variable	Total	Average LOS (SD), d	*P* value[a]
Total admissions	41 221		–
Sex n, (%)			
Female	19 604 (47.6)	7.7 (8.6)	.02
Male	21 617 (52.4)	7.9 (8.9)	
Age at surgery, mean (SD), y	54.4 (15.9)	–	
Race n, (%)			
White	25 747 (62.5)	7.3 (7.9)	<.001
Hispanic	2720 (6.6)	10.0 (11.6)	
Black or African American	2186 (5.3)	10.8 (13.2)	
Other/Not reported	988 (2.4)	9.7 (9.4)	
Asian	763 (1.9)	9.7 (11.5)	
American Indian/Alaska native	142 (0.3)	9.3 (11.7)	
Missing	8675 (21.0)	7.4 (7.2)	
Elective surgery, n (%)			
Yes	23 544 (57.1)	5.7 (7.1)	<.001
No	17 616 (42.7)	10.6 (9.8)	
Missing	61 (0.2)	8.8 (6.4)	
Admission quarter, n (%)			
1	9531 (23.1)	7.7 (8.3)	.28
2	9423 (22.9)	7.6 (8.4)	
3	9546 (23.2)	7.7 (8.6)	
4	9321 (22.6)	7.9 (9.0)	
Missing	3400 (8.2)		
Comorbidities			
Diabetes, n (%)			
Yes	5140 (12.5)	9.5 (10.0)	<.001
No	35 663 (86.5)	7.5 (8.5)	
Missing	418 (1.0)	7.9 (11.1)	
Congestive heart failure, n (%)			
Yes	731 (1.8)	12.8 (10.9)	<.001
No	40 072 (97.2)	7.7 (8.6)	
Missing	418 (1.0)	7.9 (11.1)	
Hypertension, n (%)			
Yes	16 213 (39.3)	8.4 (8.2)	<.001
No	24 590 (59.7)	7.4 (9.0)	
Missing	418 (1.0)	7.9 (11.1)	
Metastatic cancer, n (%)			
Yes	2070 (5.0)	8.5 (7.3)	<.001
No	38 733 (94.0)	7.8 (8.8)	
Missing	418 (1.0)	7.9 (11.1)	
Weight loss, n (%)			
Yes	735 (1.8)	20.8 (18.4)	<.001
No	40 068 (97.2)	7.6 (8.2)	
Missing	418 (1.0)	7.9 (11.1)	
Sodium abnormality, n (%)			
Yes	2852 (6.9)	14.8 (14.2)	<.001
No	38 369 (93.1)	7.3 (7.9)	
Missing	0 (0)	–	
Alcohol abuse, n (%)			
Yes	615 (1.5)	10.7 (10.6)	<.001
No	40 606 (98.5)	7.8 (8.7)	
Missing	0 (0)	–	
Pneumonia, n (%)			
Yes	696 (1.7)	23.7 (20.5)	<.001
No	40 525 (98.3)	7.5 (8.1)	

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TABLE 1. *continued*

Variable	Total	Average LOS (SD), d	*P* value[a]
Missing	0 (0)	–	
Esophageal varices, n (%)			
Yes	5 (0.01)	9.4 (6.0)	.19
No	41 216 (99.99)	7.8 (8.7)	
Missing	0 (0)	–	
Previous PCI, n (%)			
Yes	673 (1.6)	7.1 (5.8)	.40
No	40 548 (98.4)	7.8 (8.8)	
Missing	0 (0)	–	
Previous cardiac surgery, n (%)			
Yes	736 (1.8)	7.76 (6.9)	.001
No	40 485 (98.2)	7.80 (8.8)	
Missing	0 (0.0)	–	
History of TIA or stroke n (%)			
Yes	423 (1.0)	11.4 (11.5)	<.001
No	40 798 (99.0)	7.8 (8.7)	
Missing	0 (0)	–	
Pregnant at time of surgery, n (%)			
Yes	0 (0)	–	–
No	41 221 (100)	7.8 (8.7)	
Missing	0 (0)	–	
Smoker at time of surgery, n (%)			
Yes	4727 (11.5)	6.8 (6.3)	<.001
No	36 494 (88.5)	7.9 (9.0)	
Missing	0 (0)	–	
History of COPD, n (%)			<.001
Yes	2000 (4.9)	9.5 (9.4)	
No	39 221 (95.1)	7.7 (8.7)	
Missing	0 (0)	–	
History of ascites, n (%)			
Yes	0 (0)	–	–
No	41 214 (99.98)	7.8 (8.7)	
Missing	7 (.02)	15.3 (6.3)	
Dialysis at time of surgery, n (%)			
Yes	5 (0.01)	11.6 (8.6)	.15
No	41 216 (99.99)	7.8 (8.7)	
Missing	0 (0)	–	
History of bleeding disorders, n (%)			
Yes	1470 (3.6)	12.1 (12.4)	<.001
No	39 751 (96.4)	7.6 (8.5)	
Missing	0 (0)	–	
Any comorbidities, n (%)			
Yes	24 167 (58.6)	8.9 (9.6)	<.001
No	17 054 (41.4)	6.3 (7.0)	
Missing	0 (0)	–	
Comorbidity counts, n (%)			
0	17 054 (41.4)	6.3 (7.0)	<.001
1	13 301 (32.3)	7.7 (8.3)	
2-4	10 225 (24.8)	10.3 (10.8)	
5+	641 (1.5)	9.4 (11.0)	

[a]Mann–Whitney *U* test and 1-way ANOVA test for significant difference between groups. LOS, length of stay; SD, standard deviation; y, years; d, days; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

DISCUSSION

Models that accurately predict postoperative outcomes can be leveraged to improve patient care. Such models could be incorporated into and run in the background of clinical data systems or EMRs to automatically return predicted outcomes in a point-of-care setting. Ideally, our ensemble would be used to predict LOS prior to admission to aid in decision-making, including surgery scheduling. Importantly, potentially reversible predictors of LOS, such as sodium abnormalities, could be addressed prior to surgery. The ensemble also provides patients and families with information to aid in planning for work absences or postdischarge care, while also better enabling them to provide informed consent. Predictions could prove useful to nonclinicians, as well. For instance, bed managers could ensure that adequate numbers of beds are available in intensive care units for postoperative patients. Ancillary services, such as case management or social work, could also be mobilized at times that minimize delays in discharge. Although we do not study the relative accuracy of the model compared to clinician estimates of LOS, we imagine the ensemble being used as a "check" of provider intuition.

The ensemble could also be used to guide quality improvement initiatives. LOS indices, which compare expected to observed LOS, have been proposed as markers of efficiency and hospital performance. Using patient-specific predicted LOS to measure expected LOS may improve the accuracy of such indices, allowing hospitals to generate more representative quality metrics and, in reimbursement schemes that incentivize quality care, avoid punishment for taking on higher risk patients.[24]

Improving Modeling Methods

Our technique of algorithm selection and ensemble creation circumvents important limitations of traditional, regression-based modeling. First, we overcome biases associated with algorithm selection through direct comparison of a panel of ML algorithms, enabling empiric identification of the most predictive algorithms. A table describing some of the most common ML algorithms is included below (Table 3). Second, we take advantage of complementarity between classes of ML algorithms by creating an ensemble model from the most predictive algorithms, allowing us to generate the most accurate predictions for a given dataset.

We demonstrated that this guided ML ensemble technique can be used to predict LOS from preoperative patient characteristics with good accuracy on internal (RMSLE = .555, 95% CI, .553-.557) and external (RMSLE = .631) validation, demonstrating generalizability to never-before-seen data. Although we chose to predict LOS, this technique is broadly generalizable, and guided ML ensembles can be built to predict any number of medical outcomes.

Clinical Insights from ML Models

A common misconception of nonregression ML algorithms is that their underlying mechanisms are difficult to understand, making them less useful or easy to interpret than regression models. In this study, however, we demonstrate well-established ML techniques that provide comparable, if not more informative,

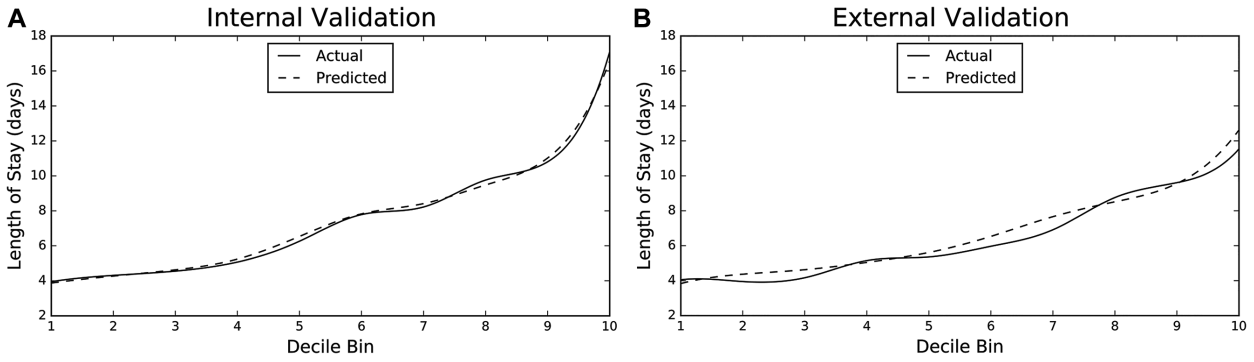


FIGURE 2. *Lift charts. Lift charts demonstrating graphically the accuracy of predicted LOS relative to actual LOS for the ensemble model on* **A**, *internal and* **B**, *external validation. Predicted LOS is divided into 10 equal bins, or deciles. Mean predicted LOS and mean actual LOS are calculated and plotted for each decile bin. Note that the lift charts reflect the fact that the average LOS in the NSQIP is shorter than the average LOS in the NIS. Solid line denotes actual LOS; dashed line denotes predicted LOS. LOS, length of stay.*

TABLE 2. Lift Chart Metrics

Internal validation (NIS)										
Decile	1	2	3	4	5	6	7	8	9	10
Predicted mean LOS, d	4.1	4.5	4.8	5.5	6.7	7.8	8.3	9.3	10.9	16.2
Actual mean LOS, d	4.2	4.3	4.6	5.0	6.8	7.6	8.5	9.8	11.0	16.7
% difference	−1.4	4.6	4.3	9.1	−1.9	2.2	−1.8	−4.8	−1.1	−3.2
External validation (NSQIP)										
Decile	1	2	3	4	5	6	7	8	9	10
Predicted mean LOS, d	3.8	4.4	4.6	5.0	5.6	6.5	7.7	8.5	9.6	12.6
Actual mean LOS, d	4.0	3.9	4.2	5.1	5.4	6.0	6.9	8.8	9.6	11.5
% difference	−5.3	10.7	11.0	−2.0	4.8	9.5	10.8	−2.8	−0.5	9.4

Description of lift chart metrics. The predicted length of stay for the internal and external validation are divided into deciles and the means calculated. This is compared to the mean for actual length of stay. LOS, length of stay; d, days.

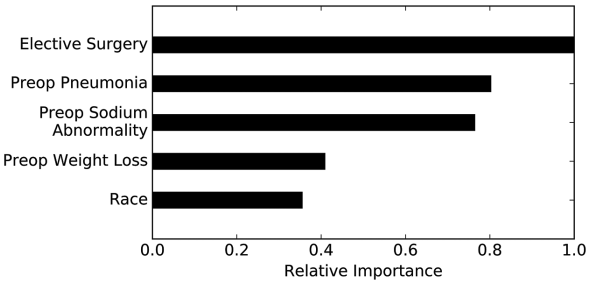


FIGURE 3. *Permutation importance. Permutation importance analyses demonstrating the relative importance of the five most influential variables on the predictions of the ensemble. The most important variable is assigned the value "1.0" and all other variables are assigned numerical values based on their importance relative to the most important variable.*

clinical insights. For example, we used permutation importance analysis to identify which of the myriad risk factors identified in univariate analysis is most important in determining extended LOS.

Partial dependence plots graphically depict the independent impact of a variable on model predictions. Plots are constructed by graphing the partial dependence "coefficient" across the entire range of values for a variable. As such, these analyses are more dynamic than regression coefficients, which remain static across the range.

Strengths and Limitations

ML techniques are often criticized for overfitting. A major strength of our study lies in the techniques we use to ensure that our ensemble predictions are not overly tailored to training data. First, we internally validate our data using five nonoverlapping cross-validation folds, generating 5 independent estimates of the ability of the ensemble to generalize to unseen data. Second,

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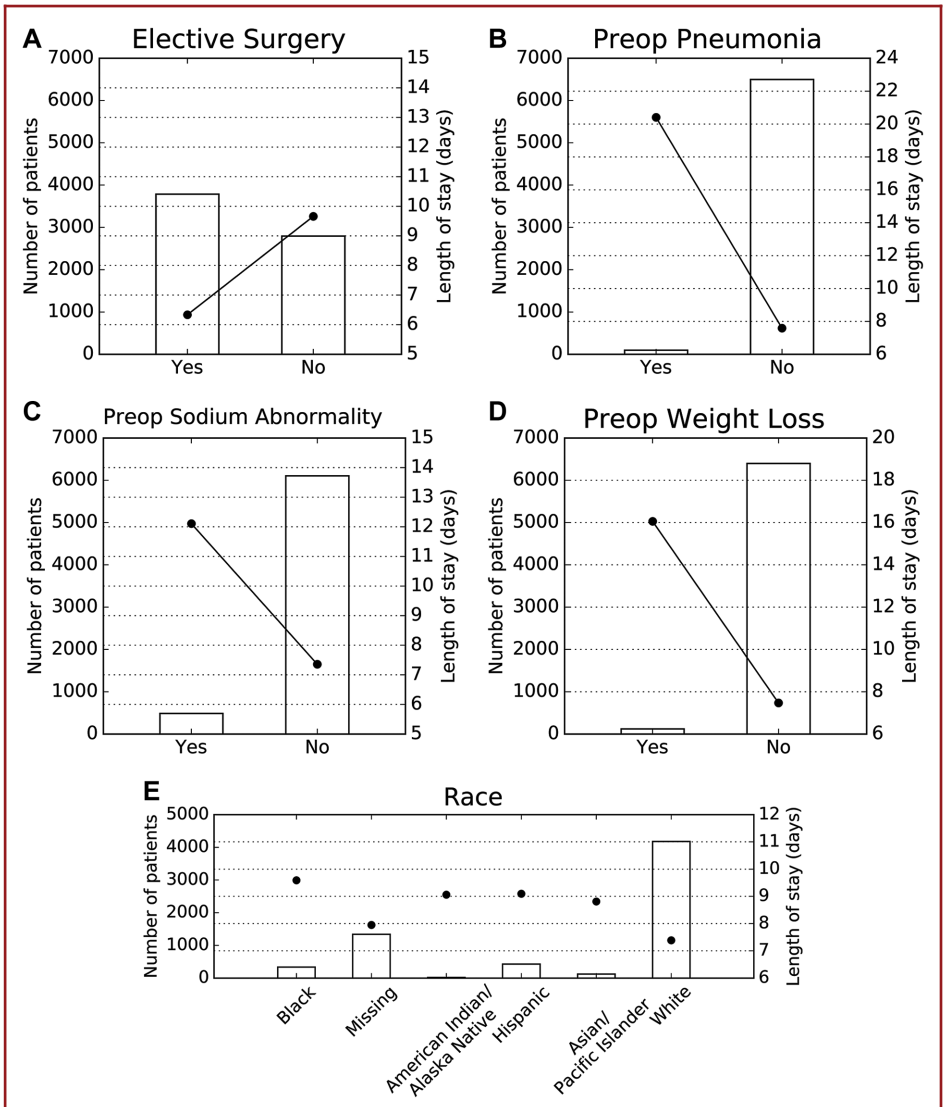


FIGURE 4. *Partial dependence plots. Partial dependence plots demonstrating the independent impact of* **A**, *elective surgery,* **B**, *preoperative pneumonia,* **C**, *preoperative sodium abnormalities,* **D**, *preoperative weight loss, and* **E**, *patient race on the ensemble model. Left Y-axis represents patient incidence for each patient group and corresponds to bars. Right Y-axis represents predicted LOS and corresponds to round heads. LOS, length of stay.*

we demonstrate generalizability to a holdout dataset never used in algorithm training. Finally, we validate the ensemble on an entirely separate database, the NSQIP.

Internal validation alone can yield overly optimistic results as testing and validation data are often very similar.[5] Demonstration of generalizability to an external dataset is therefore the gold standard for model validation, though it is rarely reported in outcomes literature.[25-26] Importantly, the populations represented in our training (NIS) and validation (NSQIP) datasets are significantly different in many respects, demonstrating that the NSQIP dataset is truly external to the NIS dataset (**Table**, **Supplemental Digital Content 2**). For example, average LOS is significantly shorter in the NSQIP than the NIS (6.5 vs 7.8 d $P < .001$). It is thus particularly remarkable that the NIS-trained ensemble can make accurate predictions from the NSQIP database with only a modest loss in performance (RMSLE = .631 vs .555). Future directions for this work include validating the ensemble on a larger external dataset, with more years represented, and validating the ensemble in a prospective fashion. It will also be important to build and validate an ensemble built from a

TABLE 3. Common ML Algorithms

Model	Description	Advantages	Disadvantages
Support vector machines	Inputs[a] are represented as vectors in higher dimensional space, with each axis corresponding to a different variable. The algorithm then calculates a plane that separates the inputs into 2 different classes. New inputs are then assigned to a class based on which side of the plane they fall on.	Can model complex, nonlinear relationships between inputs and outputs Robust to noise Fast to predict	Requires significant processing power Slow to train Kernel selection requires expertise
Artificial neural networks	Designed as a series of layers of artificial neurons, with weights assigned to every variable. Individual neurons will "fire" and propogate the signal to later layers if the weighted sum of its inputs (variables or previous neurons in the network) passes a threshold. Neural networks have been shown to be able to recognize meaningful, complex interactions in data as the number of layers increases.	Can model complex, nonlinear relationships between inputs and outputs	Difficult to interpret the underlying mechanisms driving predictions (a black box) Requires significant processing power Slow to train
K nearest neighbors	Inputs are represented as vectors in multidimensional space, with each axis corresponding to a different variable. Prediction outputs are based on the values of the *k* nearest training examples according to a specified distance metric.	Simple and easy to interpret Can be used to discriminate between many different classes, eg, tagging text No training is involved, so new training examples can be easily added. This makes the model quickly adaptable new inputs.	Slow—can take a long time to calculate nearest neighbors in large datasets. Need to know that the distance function is clinically meaningful
Generalized Additive models	Variables are fed into individual smooth functions, summed, then transformed by some (potentially nonlinear) link function into a final output.	Can more accurately represent outcomes that are not normally distributed.	Requires expertise and care in selecting appropriate link function. Effective use requires some foreknowledge of the training data.
Tree-based models			
Decision tree	Uses decision rules to classify data. Large trees may have many decision rules. Every input will be classified into 1 output value.	Easy to interpret	Prone to overfitting. Not built to maximize any objective metric.
Random forest	An ensemble of many decision trees, the output of which is determined by the mean prediction of the individual trees. The use of many trees effectively combats overfitting.	Corrects for overfitting in decision trees. Observed to perform well in a wide variety of contexts.	Optimum performance depends on tuning several important parameters.
Gradient boosted Trees	An ensemble of weak decision trees built in a stagewise manner. Subsequent trees are added according their ability to improve the model.	Observed to perform well in a wide variety of contexts.	Optimum performance depends on turning several important parameters.
Linear models			
Ordinary least Squares (logistic and linear regression)	The traditional regression technique. Finds the coefficients of a linear model that minimize the Mean Squared Error.	Easy to interpret For classification, output can be interpreted as a probability Fast to train	Assumes independently acting predictors that influence the outcome in a linear fashion.

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TABLE 3 *continued*

Model	Description	Advantages	Disadvantages
Regularized linear and regularized logistic regression	Regression that employ mechanisms to minimize overfitting by shrinking or eliminating large regression coefficients. Examples include ridge regularization, lasso regularization, and elastic net regularization (which combines ridge and lasso regularizations).	Robust to noise Easy to interpret For classification, output can be interpreted as a probability Fast to train	Assumes independently acting predictors that influence the outcome in a linear fashion.
Stochastic gradient descent	Linear model that initially assigns each variable a random coefficient. The error function of the model is then calculated, and coefficient values updated in the direction that minimizes the error function. This process continues in a stepwise manner until minimization is achieved.	Robust to noise Can be used in online-learning contexts	Susceptible to converge to suboptimal local minima
Naïve bayes	Given a training dataset, assigns probabilities that the value of a given variable is associated with the outcome of interest. Inputs are classified based on the probabilities assigned to the values of their individual variables.	Easy to understand	Assumes independently acting predictors Susceptible to outsized effects for infrequently observed data. If the frequency of classes is unbalanced in the training dataset, can have classification skewed toward the more common outcome.

[a]Inputs refers to individual patients, each of which is defined by the various variables attributable to that patient.

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single institution's data, allowing for tailoring of the ensemble to the specific practice milieu of the neurosurgeon(s) using the ensemble's predictions.[19]

Although our study has many advantages, it also has important limitations. First, because we trained our ensemble only using variables present in both the NIS and NSQIP database, there is the potential to miss important predictors that were present in only 1 of the datasets. For example, no hospital characteristics are captured in the NSQIP, a significant limitation given the importance of hospital geography as a predictor of LOS.[20] Furthermore, these datasets do not capture neurosurgery-specific variables, such as tumor characteristics. Building large, neurosurgery-specific databases will further enhance the utility of this technology in the neurosurgical sphere. Finally, our ML strategy is novel and will require further study and validation. We hope, however, that this work will encourage researchers to utilize ML in predictive modeling.

CONCLUSION

ML is a powerful, albeit underutilized, tool in clinical medicine with direct relevance to neurosurgical outcomes research. In this proof-of-concept study, we build an internally and externally validated ML ensemble model that predicts LOS following craniotomy for brain tumor. We show that clinical insights can be derived from these ML algorithms, including identification of important risk factors for extended LOS. This technique can be applied broadly to various outcomes, potentially translating into improved care for patients.

Disclosures

Mr Akagi is a data scientist employed at DataRobot Inc. Ms Muhlestein is married to Mr Akagi. Ms Muhlestein received financial support from the Vanderbilt Medical Scholars Program and the UL1 RR 024975 NIH CTSA grant. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Table. Variables included in ensemble training and external validation.

Supplemental Digital Content 2. Table. Patient characteristics for training and validation databases.

COMMENTS

In the early 1990s, the gene for Huntington's Disease was discovered, and a highly accurate test for it was developed. More than 2 decades later, most people will probably still decline to take the tests today. Why? The answer, as we all know, is a common clinical dictum: Why test for things that you cannot do something about?

One of the attractions of artificial intelligence is the ability to develop highly accurate prediction models. However, this high accuracy may not be as useful as computer scientists would make us think. They have a risk of becoming the modern-day version of genetic testing.

To make sure these new tools are actually contributing to patient care, AI projects need to incorporate concepts of modifiability in their search for predictors. But computers don't know what is modifiable and what is not. The best way (and probably the only way) to do this is to engage clinicians and health services researchers in the process. The expectation that computers can completely automate the process is unrealistic, and will likely lead to "interesting" results that may only be of interest to computer scientists, but not for clinicians taking care of patients.

There is still no substitute (yet) for the human common sense.

David Chang
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The authors have conducted a machine learning algorithm to help predict length of stay (LOS) in patients undergoing brain tumor surgery. Machine learning in predictive modelling is underutilized in medicine. Using the National Inpatient Sample (NIS) to train a variety of models and the National Surgical Quality Improvement Program (NSQIP) database for validation, the authors attain good prediction and identify several dichotomous risk factors increasing LOS, including non-elective surgery, pneumonia, sodium abnormalities, weight loss, and non-white race.

Strengths of this interesting study include the use of the NIS: predictive models generalize best when trained on large, representative datasets. External validation is the gold standard for reducing bias and overfitting; nevertheless, the authors should perform a more extensive, prospective validation going forward. While better LOS prognosticating may result in efficiency gains for hospital systems, it is unclear how these findings may be clinically meaningful.

Put to useful ends, machine learning algorithms progressively improve performance on specific tasks using specific datasets; they are beholden to the quality and generalizability of their data. Machine learning in medicine will result in large efficiency gains in detecting empirical relationships that can facilitate prediction of certain parameters.

There are many areas within neurosurgery that could benefit from better predictive modelling: in addition to providing a more accurate LOS prognosis as in this paper, machine learning algorithms could better predict rare but devastating events which are poorly suited to traditional statistical modelling - such as which aneurysms are bound to rupture; or they could assist in surgical risk assessment, or complication avoidance.

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Steroid Use Associated With Increased Odds of 30-Day Mortality in Surgical Patients With Metastatic Spinal Tumors in the Setting of Disseminated Disease

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This material was presented at Spine Summit 2018, AANS/CNS Section on Disorders of the Spine and Peripheral Nerves, March 14-17, 2018, Orlando, Florida as an Oral Presentation, General Breakout Session. The abstract will be published in *Neurosurgery Focus* per conference specifications.

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Received, February 6, 2018.
Accepted, July 10, 2018.
Published Online, August 3, 2018.

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BACKGROUND: Steroid administration is part of a standard treatment regimen in metastatic spinal cord compression, though the appropriate dose, duration, efficacy, and risks remain controversial.

OBJECTIVE: To analyze the risk of preoperative steroid use on 30-d mortality in surgical metastatic spinal tumors with dissemination disease using a large multicenter national database.

METHODS: Adult patients who underwent surgical treatment for metastatic spine tumors between 2005 and 2014 were identified in the American College of Surgeons National Surgical Quality Improvement Program database. Demographic, preoperative risk factors, operative information, and postoperative events were extracted. Multivariate logistical regression modeling was used to investigate the association with preoperative steroid use with the outcome of interest, 30-d mortality. Other independent risk factors associated with 30-d mortality were also identified.

RESULTS: Five hundred fifty-two patients underwent surgical treatment of spinal metastases with disseminated cancer present at time of surgery. Independent risk factors of 30-d mortality included prolonged steroid use (odds ratio [OR] 2.48, 95% confidence interval [CI]: 1.22-5.04, $P = .012$), dependent functional status (OR 2.91, 95% CI: 1.68-5.04, $P < .001$), history of bleeding disorder (OR 2.80, 95% CI: 1.16-6.74, $P = .021$), history of smoking (OR 2.26, 95% CI: 1.11-4.61, $P = .024$), preoperative transfusions (OR 2.91, 95% CI: 1.02-8.29, $P = .049$), and preoperative infection/sepsis (OR 2.67, 95% CI: 1.18-6.08, $P = .02$). Our model demonstrates very strong predictive capabilities, with an area under the receiver operating characteristic curve of 0.7447.

CONCLUSION: Steroid use is associated with a significant increased risk of 30-d mortality in surgical metastatic spine tumor patients with disseminated disease. These findings warrant further investigation in controlled experimental environments.

KEY WORDS: Metastases, Mortality, Spine, Steroid, Surgery

Neurosurgery 85:394–401, 2019 DOI:10.1093/neuros/nyy353 www.neurosurgery-online.com

Metastatic spinal cord compression (MSCC) develops in 5 to 10% of all cancer patients, resulting in a yearly incidence of 2.2 cases/100 000 people.[1] Once tumors reach to a metastatic status, the spine is regarded as one of the most common site of metastases.[2] Although these cases are not always seen, they are a significant cause of morbidity once metastatic tumors impede upon the neural elements or cause spinal instability.[2]

ABBREVIATIONS: ASA, American Society of Anesthesiologists; **AUC,** area under the curve; **CI,** confidence interval; **MSCC,** metastatic spinal cord compression; **NSQIP,** National Surgical Quality Improvement Program; **OR,** odds ratio; **VIF,** variance inflation factor

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Symptoms from MSCC result from direct compression on the neural elements which may cause nocturnal back pain, lower extremity weakness with possible loss of ambulation, sensory loss, and bowel or bladder dysfunction. Three mechanisms exist that explain symptom onset from this disease: local tumor expansion into the epidural space through Batson's plexus, vertebral fracture, resulting from loss of integrity of the bone caused by tumor infiltration, with fragment displacement into the epidural space, or a paraspinal mass extending into the epidural space through the neural foramina.[3] Given the profound morbidity associated with this disease, thoughtful therapeutic considerations based on input from multiple medical and surgical specialties are critical. The main objectives in treatment modalities are centered around the prevention of neurological deficit and providing spinal stability.[2]

Steroid administration is an integral part of standard treatment regimens, along with chemotherapy/radiation and/or surgical intervention.[3] Theoretically, the benefit of steroid administration results from their ability to reduce the inflammatory cascade (local inflammation, edema, and pain), to stabilize the vasculature at the site of compression, and to reduce the occurrence of neurological deficits. While it is commonplace to prescribe steroids, the appropriate dose, duration, efficacy, and risks of steroid administration remain controversial.[4-10] The reported side effects of steroid use include an increased risk of infection, decreased wound healing, psychosis, and gastric ulcer formation.[11] Upon presentation with neurological dysfunction, steroids are commonly utilized to improve neurological status for patients before more definitive intervention is attempted. However, our understanding of the dangers associated with steroid administration in patients suffering from MSCC is incomplete. The literature discusses steroid effects in small cohorts only, and as such, may not be powered appropriately to identify larger, less common associations. Using a large, national database of surgical outcomes, we analyze the risk of perioperative steroid use in the largest cohort to date and identify significant factors associated with increased 30-d mortality. We hypothesized that steroid use would have no impact on mortality in surgical metastatic spine tumor patients with disseminated disease at the time of intervention.

METHODS

Patient Identification

We collected data on surgically managed spinal oncology patients in the 2005 to 2014 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. NSQIP prospectively collects 135 patient perioperative variables, including demographic information, preoperative risk factors, operative event data, and occurrence of postoperative events within 30 d of the index procedure.[12] These variables are prospectively collected from over 600 hospitals by trained specialists using strict definitions and guidelines for inclusion of each variable to help ensure intra- and interobserver reliability.[12] The cohort for initial evaluation for inclusion in this study was generated using Current Procedure Terminology codes for procedures representing extradural neoplastic disease (63275-63278, 63300-63303).

Once identified, our cohort was narrowed further to include only those patients with current disseminated metastatic disease at the time of surgery or initial presentation, as indicated by the NSQIP variable "Disseminated Cancer". This population was then divided into the final cohorts for analysis based on use of steroids (>10 d within the previous 30 d before surgery), dichotomized as either "yes" received steroids or "no" did not receive steroids. See Supplemental Methods: Patient Identification in **Supplemental Digital Content**, for more details.

Our institutional review board has exempted this study from review since it utilizes a nationally available database that does not include any personal health information identifiers.

Data Collection

Relevant demographic, preoperative, operative, and postoperative information was collected on eligible patients who met inclusion criteria for statistical analysis. Demographic information included age, sex, race, body mass index, year of operation, and in-depth comorbidity profiles. Select comorbidities are shown in Table 1. Operative information and postoperative events were also captured. See Supplemental Methods: Data Collection in **Supplemental Digital Content**, for more details.

Statistical Analysis

The primary outcome of interest, 30-d mortality, was treated as a binomial variable to allow for logistical regression analysis. The independent variables were treated as categorical (American Society of Anesthesiologists [ASA] classification, functional status, age), continuous or were dichotomized to "yes" or "no" when appropriate. Variables such as operative time, anesthetic time, and length of stay were analyzed as continuous variables (age was also evaluated using a continuous variable in addition to the categorical variable to ensure proper fit of the variable to data behavior was captured). We ensured all logistical regression model assumptions were met.

Descriptive statistics (chi-squared/Fisher's exact test and *t*-tests) were performed to identify imbalances between the steroid and nonsteroid cohorts in our patient series. The association between steroid administration and 30-d mortality was initially analyzed using chi-squared analysis to evaluate the frequency of mortality between steroid and nonsteroid cohorts. This association was further characterized using univariate logistical regression, obtaining an odds ratio (OR). The association between other preoperative variables (demographics and comorbidities) and 30-d mortality were analyzed for significance. Multivariable logistical regression provided analysis of 30-d mortality considering the variables found to be independently significant in univariate analysis ($P < .1$), variables concerning for possible influence or potential confounding on associations with survival given prior clinical knowledge, or variables found to be imbalanced between the steroid and non-steroid cohort. Multivariate model building was conducted in both forward and reverse stepwise selection using maximum-likelihood ratio testing for between model comparisons, evaluating for significant differences in data behavior representation, and Wald testing for independent variable significance to the overall fit of the final regression model. Variables were considered significant in multivariate regression based on logistical regression OR with 95% confidence intervals (CI) that did not include unity, and *P*-values less than .05.

The Hosmer-Lemeshow test was performed to evaluate for lack of fit of the model to the behavior of the data. The C-statistic was calculated to assess the predictive capacity of our final logistical regression model. Collinearity between independent variables in the final model

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TABLE 1. Characteristics of Study Cohorts by Steroid Use Status

Characteristic	Steroid Use, No. (%)		
	No	Yes	χ2/Fisher's exact
Demographics			
Age of participants, yr			
10-19	1 (0.22)	0 (0.00)	$P = .127$
20-29	14 (3.04)	3 (3.30)	
30-39	14 (3.04)	5 (5.49)	
40-49	48 (10.41)	19 (20.88)	
50-59	125 (27.11)	17 (18.68)	
60-69	147 (31.89)	28 (30.77)	
70-79	79 (17.14)	12 (13.19)	
80-89	33 (7.16)	7 (7.69)	
Sex			
Female	161 (34.92)	23 (25.27)	$P = .074$
Male	300 (65.08)	68 (74.73)	
Race			
White	333 (72.23)	70 (76.92)	$P = .083$
Black	52 (11.28)	13 (14.29)	
Asian	13 (2.82)	4 (4.40)	
American Indian	1 (0.22)	1 (1.10)	
Native Hawaiian	1 (0.22)	0 (0.00)	
Unknown	61 (13.23)	3 (3.30)	
Select comorbidities			
Hypertension			
No	241 (52.28)	45 (49.95)	$P = .622$
Yes	220 (47.72)	46 (50.55)	
Diabetes			
No	412 (89.37)	80 (87.91)	$P = .683$
Yes	49 (10.63)	11 (12.09)	
History of COPD			
No	435 (94.36)	86 (94.51)	$P = .956$
Yes	26 (5.64)	5 (5.49)	
History of congestive heart failure			
No	457 (99.13)	91 (100)	$P = .485$
Yes	4 (0.86)	0 (0.00)	
Preoperative functional status			
Independent	389 (84.38)	66 (72.53	$P = .025$
Partially dependent	66 (14.32)	23 (25.27)	
Totally dependent	6 (1.30)	2 (2.20)	
History of bleeding disorder			
No	429 (93.06)	79 (85.81)	$P = .044$
Yes	32 (6.94)	12 (13.19)	
ASA Classification			
ASA I	1 (0.22)	0 (0.00)	$P = .335$
ASA II	58 (12.50)	8 (8.70)	
ASA III	315 (68.33)	59 (64.84)	
ASA IV	86 (18.66)	23 (25.27)	
ASA V	1 (0.22)	1 (1.10)	
Operative variables			
Site of surgery			
Cervical	68 (14.75)	17 (18.68)	$P = .318$
Thoracic	255 (55.31)	54 (59.34)	
Lumbar	120 (26.03)	19 (20.88)	
Sacral	18 (3.90)	1 (1.10)	
Emergent surgery			
No	383 (83.08)	72 (79.12)	$P = .364$
Yes	78 (16.92)	19 (20.88)	
Type of surgery			
Laminectomy	354 (76.79)	66 (72.53)	$P = .384$
Corpectomy	107 (23.21)	25 (27.47)	

ASA, American Society of Anesthesiologists; χ2, chi-squared test, Fisher's exact test; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

was evaluated using the variance inflation factor (VIF) and creating a correlation matrix. Mantel-Haenszel investigations were used to evaluate for any confounding or treatment effect modification the independent variables in the final logistical regression model might have on the effect of steroid use on 30-d mortality. Direct variable interactions were analyzed using logistical regression and evaluated for statistical significance.

The relationship between steroid use and other postoperative adverse events was analyzed using chi-squared/Fisher exact test and logistic regression. These postoperative complications were then analyzed for their influence on 30-d mortality to identify the association between steroid use, the complication occurrence, and 30-d mortality to elaborate on possible associations. Cases with missing information for variables of interest were deleted in a listwise deletion method.

All statistical analyses were performed using STATA 14.0 (STATACORP, College Station, Texas).

RESULTS

From 2005 to 2014, we identified 1262 surgical spinal tumor patients, 556 of these patients having disseminated disease at the time of surgery. Of these, 2 patients were dropped for missing functional status, and 2 patients dropped for missing ASA Classification information. A total of 552 patients met all inclusion criteria, with 91 (16.5%) receiving preoperative steroids. Thirty-day mortality was identified in 51 patients, 16 of the steroid cohort (17.6% of patients receive steroids) and 35 of nonsteroid cohort (7.6% of patients who did not receive steroids). Patient demographics and select comorbidities are shown in Table 1.

Chi-Squared Analysis

Analysis of preoperative steroid use and 30-d mortality using chi-squared testing revealed a statistically significant association between steroid use and increased mortality compared to the nonsteroid cohort (17.4% vs 7.7%, $P = .004$). Other baseline characteristics were evaluated for imbalance. The steroid use cohort was found to have significantly higher proportion of patients with partial/totally dependent functional status

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TABLE 2. Significant Variables on Univariate Analysis of Mortality in Patients With Disseminated Cancer

Variable	Odds ratio	95%	CI
Preoperative characteristics			
ASA Classification	2.75	1.66	4.55
Smoker	2.01	1.08	3.74
Preoperative functional status	3.44	2.06	5.73
History of bleeding disorder	2.81	1.27	6.22
Preoperative steroid use	2.6	1.32	4.73
Emergent surgery	2.81	1.51	5.21
Intraoperative factors			
Intraoperative blood product transfusion	3.56	1.44	8.87
Reintubation	19.44	5.48	68.95
Sepsis	3.14	1.53	6.41
Postoperative events			
Pneumonia	3	1.15	7.81
MI/cardiac arrest	7.65	1.67	35.18
Deep wound infection	3.47	1.21	9.96

ASA, American Society of Anesthesiologists; CI, confidence interval; MI, myocardial infarction.

TABLE 3. Covariates in the Multivariate Regression Models

Variable	Odds Ratio	95% CI	*P*-Value
Perioperative risk factor regression			
Dependent functional status	2.91	1.68-5.04	<.001
Steroid use	2.48	1.22-5.04	.012
COPD	1.78	0.60-5.27	.3
CHF	3.41	0.36-32.17	.3
History of bleeding disorder	2.8	1.16-6.74	.021
Smoker	2.26	1.11-4.61	.024
Preoperative transfusion	2.91	1.02-8.29	.049
Preoperative infection/sepsis	2.67	1.18-6.08	.02
Hypertension	1	0.50-2.00	.9
Diabetes	0.72	0.25-2.11	.5
Sex	1.4	0.67-2.94	.4
Age	1.16	0.89-1.50	.3
ASA III-V	1.21	0.38-3.88	.7
Operative factor regression			
Emergent case	2.28	1.19-4.39	.013
Thoracic level	1.34	.71-2.51	.37
Corpectomy	1.8	0.78-4.16	.17
Postoperative event regression			
Unplanned reintubation	13.17	2.85-60.74	.001
Cardiac event	0.9	0.08-9.87	.9
Pneumonia	1.93	0.64-5.86	.24
Deep wound infection	3.36	1.11-10.12	.032

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

($P = .025$) and presence of a condition leading to an increased risk of bleeding ($P = .044$).

Univariate Logistical Regression

Univariate logistical regression evaluated the association between preoperative steroid use and 30-d mortality. The other specified variables of interest were then evaluated for independent statistical significance as they relate to 30-d mortality. The significant variables ($P < .10$) are shown in Table 2. Steroid use resulted in OR of death of 2.60 (95% CI: 1.37-4.93, $P = .003$). These significant variables were utilized to build multivariable logistical regression models.

Multivariate Logistical Regression

Preoperative Factor Analysis

In the preoperative regression model, steroid use was significantly associated with an increased odds of mortality (OR 2.48, 95% CI: 1.22-5.04, $P = .012$). Other independently significant covariates included dependent functional status (OR 2.91, 95% CI: 1.68-5.04, $P < .001$), history of bleeding disorder (OR 2.80, 95% CI: 1.16-6.74, $P = .021$), history of smoking (OR 2.26, 95% CI: 1.11-4.61, $P = .024$), preoperative transfusion (OR 2.91, 95% CI: 1.01-8.29, $P = .049$), and preoperative infection/sepsis (OR 2.67, 95% CI: 1.18-6.08, $P = .02$). The variables from the full logistic model can be seen in Table 3 and are summarized in Figure 1.

Investigations into direct interaction effects between steroid use and the other significant variables in this model did not reveal any significant influence on the association between steroid use and increased mortality. Collinearity was assessed using the VIF with a mean VIF for the model was 1.04, reassuring that the effect of steroid is not due to collinearity with another variable (see Table: Variance Inflation Factor analysis for Collinearity in **Supplemental Digital Content**, providing full VIF profile). Mantel-Haenszel investigations failed to reveal any significant interaction or confounding effect of the other covariates on steroid use (see Supplemental Results in **Supplemental Digital Content**, which describes interaction effects, confounding, and collinearity). The C-statistic was calculated to test predictive capabilities of the model on the outcome of 30-d mortality, and revealed an area under the curve (AUC) of .744, representing a strong predictive capacity of the final logistical model (Figure 2). The Hosmer-Lemeshow test did not reveal a lack of fit of our model ($P = .8$); thus, our model fit the behavior of the data well and retained strong predictive capacity of 30-d mortality in patients with MSCC and disseminated cancer at the time of intervention.

Intraoperative/Postoperative Factor Analysis

Operative characteristics and postoperative events were evaluated for effects on mortality. In the operative characteristic logistical regression model, only emergent status of the surgery was significant (OR 2.28, 95% CI: 1.19-4.39, $P = .013$). In the postoperative model, reintubation (OR 13.17, 95% CI: 2.85-60.74, $P = .001$) and deep wound infection (OR 3.35, 95% CI 1.13-10.12, $P = .032$) were significantly associated with 30-d mortality. There was no evidence of collinearity or modification

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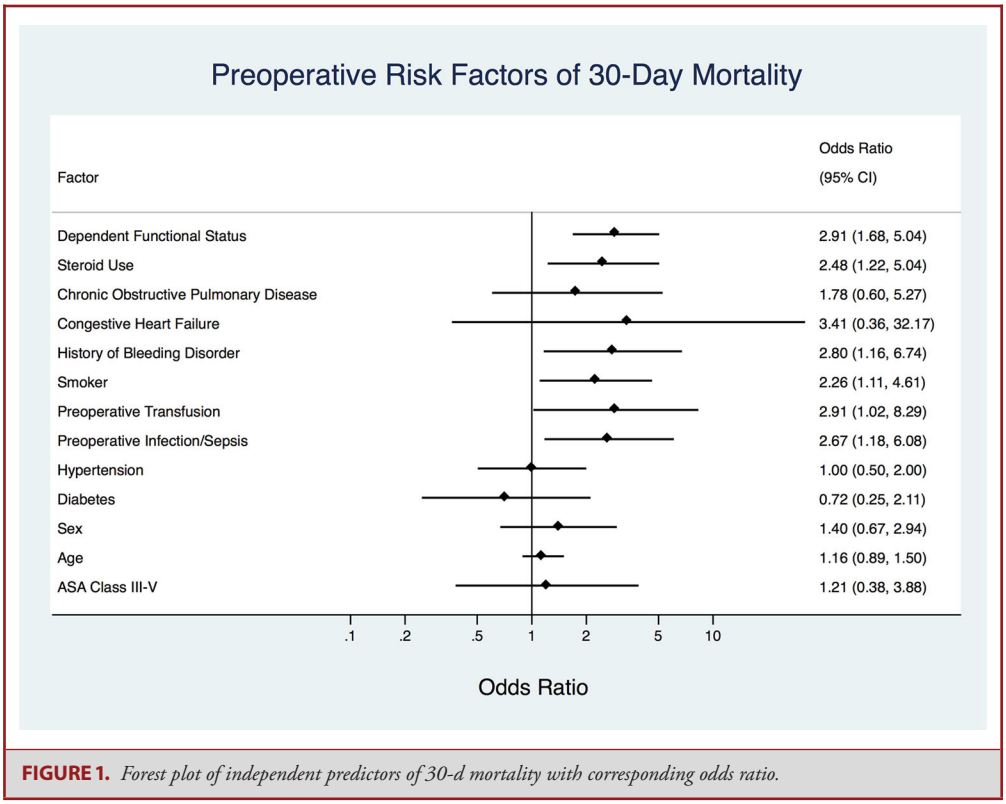


FIGURE 1. *Forest plot of independent predictors of 30-d mortality with corresponding odds ratio.*

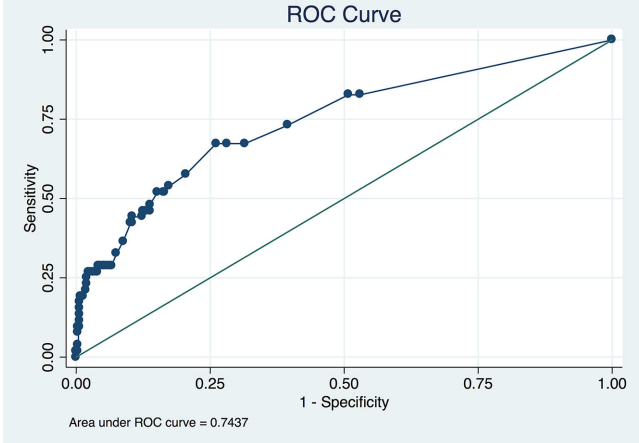


FIGURE 2. *Receiver operating characteristic (ROC) curve showing the ability to predict 30-d mortality based on the multivariable model.*

of the steroid variable's association with 30-d mortality. Steroid use was significantly associated with deep wound infection ($P < .001$); however, this did not have any confounding or effect modification of steroid's association with mortality. Controlling for the deep wound infections, steroids remained independently significantly associated with 30-d mortality with an increased odds of death by a factor or 2.36 (95% CI: 1.22-4.56, $P = .010$), while deep wound infection became insignificant ($P = .07$) (see Table 4).

A final, all-encompassing model, controlling for all significant risk factors (preoperative, operative, and postoperative), demonstrated that steroid use still remained significant. There was no evidence of significant interaction, confounding, or collinearity between steroid use and any other variable in our study, and showed a very similar stronger association with 30-d mortality (OR 2.60, 95% CI: 1.12-5.63, $P = .015$) compared with the preoperative model (see Table: Covariates in the "All-Inclusive" Multivariate Regression Model in **Supplemental Digital Content**, for the full model).

DISCUSSION

We sought to investigate the relationship between preoperative steroid use and 30-d mortality in surgically managed metastatic spinal oncology patients with disseminated disease. We focused on steroid use and associated analysis of preoperative characteristics and treatment profiles to identify possible modifiable risks factors that may be augmented to improve patient outcomes prior to definitive treatment of the spinal metastases.

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TABLE 4. Association of Complications by Steroid Use Status

	Steroid use		
	No. (%)		
Complication	No	Yes	χ2/Fisher's exact
Superficial wound infection			
No	452 (98.5)	90 (98.9)	$P = .6$
Yes	9 (1.5)	1 (1.1)	
Deep wound infection			
No	450 (97.6)	82 (90.1)	$P < .001$
Yes	11 (2.4)	9 (9.9)	
Pneumonia			
No	439 (95.2)	86 (94.5)	$P = .8$
Yes	22 (4.8)	5 (5.5)	
Wound dehiscence			
No	454 (98.5)	90 (98.9)	$P = .8$
Yes	7 (1.5)	1 (1.1)	
Urinary tract infection			
No	439 (95.2)	88 (96.7)	$P = .5$
Yes	22 (4.8)	3 (3.3)	
Deep vein thrombosis			
No	430 (93.3)	89 (97.8)	$P = .1$
Yes	31 (6.7)	2 (2.2)	
Pulmonary embolism			
No	453 (98.3)	91 (100)	$P = .2$
Yes	8 (1.7)	0	
Preoperative infection/sepsis			
No	416 (90.2)	81 (89.0)	$P = .7$
Yes	45 (9.8)	10 (11.0)	

There were no incidences of postoperative sepsis/septic shock in this cohort.

Among the 552 patients in our study, 51 (9.3%) died within the 30-d postoperative window. When stratified by cohort (steroid vs nonsteroid use), the incidence of mortality was much greater among patients receiving prolonged preoperative steroids compared to those who did not (17.6% vs 7.6%). With strong predictive capabilities and an excellent fit of the data, our model revealed steroid use conferred a significant independent risk of 30-d mortality in the patient population studied (OR: 2.48, 95% CI: 1.22-5.04, $P = .012$). In addition to steroid use, dependent functional status, history of a bleeding disorder, and preoperative infection/sepsis were independent risk factors of 30-d mortality. There was no collinearity nor confounding effect of the covariates upon each other in the model.

This study represents the initial identification of the association between preoperative steroid administration and increased odds of 30-d mortality in surgically managed metastatic spinal oncology patients with disseminated cancer.

We considered this finding quite surprising. Our initial concern was this finding may be partially due to collinearity with another variable in the model (eg, functional status), or the result of positive confounding, which would make the effect of steroid use appear larger statistically. This was important to investigate further given the association between use of preoperative steroids with dependent functional status and history of bleeding disorder; however, no significant collinearity or confounding was present. Thus, each significant covariate independently conveys an increased risk of 30-d mortality.

We conducted additional exhaustive statistical analysis, looking for any evidence that the association between steroid use and mortality was factitious. However, we found none. We pursued statistical diagnostics including evaluation of logistical regression model assumptions, covariate behaviors and interactions (collinearity, correlation, confounding, effect modification, etc.), predictive capability of the model, and model fit to the behavior of the data. We did not find any evidence to suggest the associations identified are spurious. In our data set obtained from the NSQIP database, the association between preoperative steroid use and increased 30-d mortality is significant and real. Our model, after calculating the C-statistic with an associated AUC = 0.7447 and an H-L statistic of 0.8, not only fits the data very well, but also has strong predictive capacity of 30-d mortality.

For further clarification, we investigated operative and postoperative factors and their effect on 30-d mortality to further distinguish the relationship between steroid use and mortality. Specifically, we investigated the effects of these variables to look for any association with or confounding of the relationship between steroid use and mortality. This, however, is admittedly outside of the scope of the initial hypothesis, and in fact, encompasses a fundamentally different experimental question (our initial evaluation was to identify modifiable preoperative factors). The operative factor logistical regression model found only emergent status as significant (OR 2.28, 95% CI: 1.19-4.39, $P = .013$), while corpectomy vs laminectomy (reference) and thoracic location of surgery did not significantly affect mortality. The postoperative event logistical regression model identified re-intubation (OR 13.17, 95% CI: 2.85-60.74) and deep wound infection (OR 3.35, 95% CI: 1.11-10.12) as significantly associated with 30-d mortality, where cardiac events and pneumonia were not. The model covariates and associated estimates can be seen in Table 3. The steroid variable was tested in these models to evaluate for presence of collinearity or confounding effect with none identified.

Finally, an all-encompassing model of all cohort characteristics was modeled to assess for association with 30-d mortality. This allowed for a "big picture" analysis and ensured that no other covariate (preoperative, operative, or postoperative) was responsible for the effect seen when evaluating steroid use. Steroid use remained an independently significant risk factor for 30-d mortality. This again is different than the initial hypothesis and answers a different question; however, given the antithetical findings of our study to current practice,[13] we felt the investigation was warranted for scientific completeness. In this model, steroid use revealed a similar independent risk of death, with an OR of 2.60 (95% CI:1.12-5.63, $P = .015$)

compared to OR = 2.48 in the preoperative only model. This suggests that in the overall picture, the effect of steroid on mortality is independent of other preoperative, operative, and postoperative characteristics and events, as the OR remained stable when controlling for all the corresponding covariates.

The literature describes correlations between corticosteroid administration in MSCC patients and severe adverse effects. However, there has been no statistically significant data demonstrating that the use of corticosteroid in MSCC treatment increases mortality in humans.[5-7,11,14,15] A recent systematic review of the literature investigated steroid dose and benefit gained but it failed to yield conclusive results.[16] The review did, however, show dose-related correlations with severe toxicities (gastrointestinal bleeding and perforation).[16] Both previous animal studies and human studies in nonsurgical cohorts have identified toxicities and complications of steroid use, but only animal studies have identified evidence of mortality.[8-10]

Additionally, a recent Cochrane review of the management of patients with metastatic spinal cord compression revealed there is no evidence that steroid use is better than no steroid use in the management of these patients.[4] What we are left with is no evidence-based results that show steroids are effective, with studies that show they may be harmful, yet we continue to use them as an integral part of management. This lack of evidence of benefit with our findings of harmful associations warrants further causal explanatory investigations into the association identified between preoperative steroid use and increased 30-d mortality in this surgical cohort.

Limitations

It is important to view the results of this study in light of its limitations. Several limitations exist when using large databases to answer scientific hypotheses. Even though NSQIP data are collected prospectively, this type of investigation constitutes a retrospective analysis of the prospective data. This methodology is at risk for selection bias, as hospitals are not required to report all consecutive cases. The authors attempted to mitigate this risk as much as possible by using very specific inclusion criteria. However, there remains inherent selection bias in databases that cannot be mitigated by statistical and methodological approaches and must be tolerated to utilize this type of data for analysis. The steroid variable in NSQIP itself is somewhat vague and at risk of misclassification of exposure bias. However, there is precedent in the literature using this variable to represent steroid use.[17] Additionally, there is no information regarding dose, duration, pulsatile vs nonpulsatile administration, and we cannot control for this statistically. We cannot speak to the dosing of steroids (stable vs tapering, high vs low) in the association identified between steroid use and 30-d mortality.

NSQIP also does not provide indications for steroid administration nor causes of death, so there is an amount of tolerance given to this study's findings, though chronic conditions that normally use steroids (chronic obstructive pulmonary disease, asthma, etc) were evenly distributed between cohorts and inhalation or topical administrations are not included in the variable. This information increases the likelihood that steroids were administered for the MSCC disease itself (see Supplemental Limitations in **Supplemental Digital Content**, for further discussion on limitations).

CONCLUSION

Steroid use is associated with an increased risk of 30-d mortality (OR 2.48, 95% CI: 1.22-5.04, $P = .012$) in surgically metastatic spine tumor patients with disseminated disease at the time of intervention. While this outcome must be viewed in light of the methods used, the true risk of steroids in this type of surgical patient must be evaluated further. This surprising finding warrants further, controlled studies, to investigate further into the association identified in this study.

Disclosures

Dr Mehta has provided consulting services to Spinal Elements, and received teaching travel funding from Globus. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. The Supplemental Digital Content expands on: Methods: Patient Identification; Methods: Data Collection; Results: Interaction effects, Confounding, and Collinearity; and Limitations. Table 1, Variance Inflation Factor Analysis for Collinearity. Table 2, Covariates in the "All-Inclusive" Multivariate Regression Model.

Acknowledgments

American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the American College of Surgeons NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The authors would like to thank the Department of Public Health and the Department of Statistics at The University of Chicago for providing guidance regarding the appropriate utilization of statistical methods and ensuring the validity of the results derived.

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Risk Factors Associated With 90-Day Readmissions After Degenerative Lumbar Fusion: An Examination of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Registry

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Portions of this study were presented as an abstract at the 2018 AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves Annual Meeting (Orlando, Florida, March 17, 2018) and the 2018 AANS Annual Scientific Meeting (New Orleans, Louisiana, April 30, 2018).

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Received, March 27, 2018.
Accepted, July 11, 2018.
Published Online, August 3, 2018.

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BACKGROUND: Most studies have evaluated 30-d readmissions after lumbar fusion surgery. Evaluation of the 90-d period, however, allows a more comprehensive assessment of factors associated with readmission.

OBJECTIVE: To assess the reasons and risk factors for 90-d readmissions after lumbar fusion surgery.

METHODS: The Michigan Spine Surgery Improvement Collaborative (MSSIC) registry is a prospective, multicenter, and spine-specific database of patients surgically treated for degenerative disease. MSSIC data were retrospectively analyzed for causes of readmission, and independent risk factors impacting readmission were found by multivariate logistic regression.

RESULTS: Of 10 204 patients who underwent lumbar fusion, 915 (9.0%) were readmitted within 90 d, most commonly for pain (17%), surgical site infection (16%), and radicular symptoms (10%). Risk factors associated with increased likelihood of readmission were other race (odds ratio [OR] 1.81, confidence interval [CI] 1.22-2.69), coronary artery disease (OR 1.57, CI 1.25-1.96), ≥4 fused levels (OR 1.41, CI 1.06-1.88), diabetes (OR 1.34, CI 1.10-1.63), and surgery length (OR 1.09, CI 1.03-1.16). Factors associated with decreased risk were discharge to home (OR 0.63, CI 0.51-0.78), private insurance (OR 0.79, CI 0.65-0.97), ambulation same day of surgery (OR 0.81, CI 0.67-0.97), and spondylolisthesis diagnosis (OR 0.82, CI 0.68-0.97). Of those readmitted, 385 (42.1%) patients underwent another surgery.

CONCLUSION: Ninety-day readmission occurred in 9.0% of patients, mainly for pain, wound infection, and radicular symptoms. Increased focus on postoperative pain may decrease readmissions. Among factors impacting the likelihood of 90-d readmission, early postoperative ambulation may be most easily modifiable. Optimization of preexisting medical conditions could also potentially decrease readmission risk.

KEY WORDS: Adverse events, Complications, Lumbar fusion, Readmissions, Registries, Risk factors, Spine

Neurosurgery 85:402–408, 2019 DOI:10.1093/neuros/nyy358 www.neurosurgery-online.com

In the United States, there has been an ongoing growth in fusion surgeries, which has been attributed to a number of factors, including the aging population.[1-4] This trend is evidenced by the 2.7-fold increase in hospital discharges after lumbar spine fusion that occurred between 1998 and 2008.[5] Although most patients undergo lumbar fusion without incident, complications are an unfortunate reality that can negatively impact recovery.[6] Reported complications are varied and include durotomy, seroma, hematoma, infection, and

ABBREVIATIONS: ASA, American Society of Anesthesiologists; **BCBSM,** Blue Cross Blue Shield of Michigan; **BCN,** Blue Care Network; **CAD,** coronary artery disease; **COPD,** chronic obstructive pulmonary disease; **DVT,** deep venous thrombosis; **LOS,** length of stay; **MSSIC,** Michigan Spine Surgery Improvement Collaborative; **NSQIP,** National Surgical Quality Improvement Program; **ORs,** odds ratio; **SSI,** surgical site infection; **QOD,** Quality and Outcomes Database

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medical problems such as deep venous thrombosis (DVT), pulmonary embolus, and urinary tract infection, among others.[7-9]

After discharge, the development of an adverse event can result in readmission to the hospital. Beyond the negative impact on the patient, readmission is expensive and has become a focus for cost containment.[6,10-13] To date, studies have predominantly focused on 30-d readmissions after lumbar surgery, with reported rates ranging from 4.4% to 7.3%.[14-21] However, complications can develop over a longer interval resulting in readmission after 30 d. To more comprehensively evaluate factors impacting readmission, analysis over a 90-d period has been advocated.[22] Analysis beyond the 30-d period has been shown to result in higher readmission rates and further investigation may find differing causes and risk factors. In one recent study evaluating 90-d readmission after lumbar fusion, a 24.8% rate was observed.[23]

Whether 30-d or 90-d readmission is evaluated, the data for many of these analyses have been derived from Medicare claims data or from databases such as the American College of Surgeons National Surgical Quality Improvement Program (NSQIP).[16-21] Although these databases contain large numbers of patients, there are significant disadvantages, since the data collected are not specifically related to spinal surgery. Factors related to readmission for spine surgery may not be included in the data sets, and variables predictive of readmission in spine surgery may be coded differently or missing in the more generic databases than in a spine-specific database; these factors have been shown to affect the results of orthopaedic and spine surgery outcome studies derived from these and similar databases.[24-33] Although there have also been readmission studies based on spine-specific patient databases, these are typically single-institution investigations that are limited by their sample size and generalizability.[34-36]

Founded in 2013, the Michigan Spine Surgery Improvement Collaborative (MSSIC) established a prospective, longitudinal, multicenter quality improvement registry of patients undergoing cervical and lumbar surgery, with the goal to enhance clinical outcomes and manage cost.[37] The aim of this study is to analyze the MSSIC registry to determine rates of 90-d readmissions after lumbar fusion surgery and the risk factors associated with these readmissions.

METHODS

After approval by the Henry Ford Hospital Institutional Review Board, data from the MSSIC registry were queried for retrospective analysis. MSSIC is funded by Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network (BCN; Grand Rapids, Michigan) as part of their Value Partnerships program. Funding is used to support the coordinating center staff, the registry, and hospital-based abstractors at each participating hospital. Presently, there are 26 participating hospitals. Quarterly meetings, attended by surgeon "champions" from participating centers as well as data abstractors and coordinating staff, are held to review data and organize and monitor quality improvement initiatives.

TABLE 1. Selectable Options for the Abstractor Within the MSSIC Registry

Reason for readmission
Deep venous thrombus
Pulmonary embolism
Myocardial infarction
Stroke
Urinary tract infection
SSI
Surgical site hematoma
Neurogenic bowel/bladder
A new neurological deficit (cerebrovascular accident, CVA) with confirmation of stroke on magnetic resonance image
A new spine-related lower extremity motor deficit (not CVA)
A new neuro deficit related to cervical spinal cord or nerve injury
A new spine-related radicular finding of numbness, pain, or weakness
Pain
Other
Not related to previous noted complications

The MSSIC registry focuses on cervical and lumbar surgery for degenerative diseases. Diagnoses related to tumor, deformity, infection, and trauma are excluded. Data consisting of pertinent past medical history, surgical indications, surgical procedure and in-hospital characteristics, and both perioperative and later (90-d) complications, as well as documented readmissions, are abstracted from medical records by trained, full-time records abstractors with data quality and completeness assured by annual formal data quality audits. Patient-reported outcomes are assessed at 90 d, 1 yr, and 2 yr postsurgery (with the same scales used for baseline presurgical assessment) and include the EQ5D, 0 to 10 NRS for pain, and Oswestry Disability Index. Within the MSSIC registry, commonly reported causes for readmission (ie, DVT) are selectable options for the abstractors based on chart review. In addition, an "other" option is selectable for causes that are not listed within the registry (Table 1). More than 1 reason can be given for the cause for readmission. Patients admitted for any other planned surgery within the 90-d period after the index spinal surgery were not counted as readmitted within the MSSIC registry.

Statistical Analysis

Univariate comparisons of patient and operative characteristics between patients with and without readmissions were performed. Chi-square tests were used for categorical variables, *t*-tests were used for normally distributed continuous variables, and Wilcoxon rank-sum tests were used for skewed, continuous variables. The logistic regression model was constructed with readmission as the outcome and patient/operative characteristics as the predictor variables. All patient/operative characteristics considered in the univariate comparisons were included in the multivariable logistic model. ORs (odds ratios) >1 implied that a predictor variable was associated with increased odds of having a readmission, while those <1 implied decreased odds. A P-value $< .05$ was considered significant. All analyses were performed using R version 3.3.2 (R Project for Statistical Computing; https://www.r-project.org; The R Foundation, Vienna, Austria).

TABLE 2. Reasons Given for Readmission[a]

Reason for readmission	n (%)
Pain	151 (17%)
SSI	142 (16%)
Radicular findings	85 (10%)
Urinary tract infection	73 (8%)
Deep venous thrombus	51 (6%)
Surgical site hematoma	43 (5%)
Pulmonary embolism	28 (3%)
Lower extremity motor deficit	22 (3%)
Myocardial infarction	17 (2%)
Urinary retention	14 (2%)
Neuro deficit with stroke	11 (1%)
Neuro deficit related to cervical spinal cord or nerve injury	6 (1%)
Neurogenic bowel/bladder	5 (1%)
Other	392 (45%)
Not related to previously noted complications	221 (25%)

[a]Multiple reasons could be given so percentages do not sum to 100.

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RESULTS

Overall, 10 204 patients who underwent lumbar fusion from February 24, 2014 to September 14, 2017 were included for analysis. The database was queried in January 2018 to allow sufficient time to obtain 90-d follow-up. The most common indication for surgery was stenosis (82%), followed by spondylolisthesis (56%) and then disc herniation (50%).

A total of 915 (9.0%) patients were readmitted within the 90-d period after surgery. Table 2 details the reasons for readmission. In many cases, more than 1 cause for readmission per patient was provided. The most frequent reason reported was the nonspecific "other." The most common specified reason for readmission was pain (17%) followed by surgical site infection (SSI; 16%). Radicular symptoms were the reason for readmission in 10% of readmitted patients. Neurological deficits were infrequent, with lower extremity weakness being the most commonly reported neurological deficit, in 3% of readmitted patients.

In the set of patient characteristics, univariate analysis showed significant associations with readmission for age, race, body-mass index, diabetes, scoliosis, history of DVT, coronary artery disease (CAD), depression, American Society of Anesthesiologists (ASA) grade, indication for surgery, preoperative ambulation, private insurance, and previous spine surgery (Table 3). For operative characteristics, the number of levels treated, surgery length, estimated blood loss, ambulation same day as surgery, length of stay (LOS), and discharge to home were all significantly different between the not-readmitted and readmitted patients (Table 4).

Table 5 shows the results of the logistic regression in which 7087 (69.5%) patients with complete data were analyzed. Race, diabetes, CAD, spondylolisthesis diagnosis, private insurance, ≥4 fusion levels, ambulation same day as surgery, surgery length, and discharged to home were found to be significantly associated with readmission. Specifically, the OR was 1.81 for "other" race, representing an 81% higher risk for readmission compared to white patients. The OR was 1.57 for CAD, 1.41 for ≥4 fused levels compared to one level, 1.34 for diabetes, and 1.09 for surgery length per hour increments representing a 57%, 41%, 34%, and 9% higher risk, respectively. Conversely, the OR was 0.63 for discharged to home, 0.79 for private insurance versus no private insurance, 0.81 for ambulation on same day as surgery vs ambulation on some later date, and 0.82 for spondylolisthesis vs nonspondylolisthesis diagnosis. These represent a 37%, 21%,

TABLE 3. Univariate Analysis of Patient Characteristics

Variable	Not readmitted (n = 9289)	Readmitted (n = 915)	*P*-value
Age in years	60.6 ± 12.8	63.4 ± 12.9	**<.001**
Male	4104 (44%)	394 (43%)	.515
Race			
White	5848 (63%)	530 (58%)	**.004**
Black	554 (6%)	74 (8%)	
Other	302 (3%)	40 (4%)	
Not documented	2585 (28%)	271 (30%)	
Body-mass index	31.1 ± 7.5	31.9 ± 7.6	**.002**
Diabetes	1739 (21%)	270 (33%)	**<.001**
Scoliosis	1812 (20%)	216 (24%)	**.003**
History of deep venous thrombus	498 (6%)	67 (8%)	**.015**
CAD	1009 (12%)	169 (21%)	**<.001**
Depression	2418 (29%)	273 (33%)	**.015**
Anxiety	1999 (24%)	223 (27%)	.050
Osteoporosis	881 (11%)	95 (12%)	.410
ASA > 2	5071 (55%)	607 (66%)	**<.001**
Indication for surgery[a]			
Disc herniation	4635 (50%)	480 (53%)	.126
Spondylolisthesis	5180 (56%)	473 (52%)	**.021**
Stenosis	7598 (82%)	757 (83%)	.419
Recurrent disc herniation	404 (4%)	25 (3%)	**.021**
Adjacent segment disease	1122 (12%)	134 (15%)	**.023**
Revision of hardware	1051 (11%)	144 (16%)	**<.001**
Clinical presentation[a]			
Axial pain	7181 (77%)	714 (78%)	.606
Radicular pain	8397 (91%)	817 (89%)	.286
Bowel/bladder dysfunction	163 (2%)	17 (2%)	.820
Weakness	2076 (22%)	223 (24%)	.161
Foot drop	281 (3%)	28 (3%)	.952
Ambulatory preoperative	6744 (79%)	563 (68%)	**<.001**
Private insurance	4112 (44%)	304 (33%)	**<.001**
Previous spine surgery	4726 (56%)	516 (61%)	**.003**

[a]More than 1 indication/symptom per patient was possible.
Bold values refers to statistical significance with $P<0.05$.

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TABLE 4. Univariate Analysis of Surgical Characteristics

Variable	Not readmitted (n = 9289)	Readmitted (n = 915)	*P*-value
Number of levels			
1	4729 (51%)	387 (42%)	**<.001**
2	2680 (29%)	251 (27%)	
3	1090 (12%)	127 (14%)	
4 or more	785 (9%)	150 (16%)	
Ambulated same day as surgery	3811 (42%)	294 (34%)	**<.001**
Surgery length (h)	2.5 (1.8, 3.5)	2.7 (2, 3.9)	**<.001**
Blood loss (cc)	200 (100, 400)	250 (100, 500)	**<.001**
LOS (d)			
0-1	852 (9%)	52 (6%)	**<.001**
2-3	5188 (56%)	400 (44%)	
4+	3249 (35%)	463 (51%)	
Discharged home	7573 (82%)	614 (67%)	**<.001**

Bold values refers to statistical significance with $P<0.05$.

TABLE 5. Logistic Model for Associations Between Patient/Operative Characteristics and Readmission (n = 7087 With Complete Data)

Variable	OR	95% Confidence Interval		*P*-value
Age	1.02	0.98	1.07	.400
Race				
White	Referent			
Black	1.31	0.95	1.81	.103
Other	1.81	1.22	2.69	**.003**
Not documented	1.09	0.89	1.34	.418
Body-mass index	1.01	1.00	1.02	.380
Diabetes	1.34	1.10	1.63	**.003**
Scoliosis	1.03	0.84	1.26	.794
History of deep venous thrombus	1.01	0.73	1.39	.958
CAD	1.57	1.25	1.96	**<.001**
Depression	1.03	0.83	1.27	.815
Anxiety	1.13	0.90	1.40	.300
Osteoporosis	0.93	0.72	1.22	.606
ASA > 2	1.02	0.84	1.24	.862
Disc herniation	1.02	0.86	1.21	.814
Spondylolisthesis	0.82	0.68	0.97	**.024**
Adjacent segment disease	1.01	0.78	1.31	.921
Revision of hardware	1.11	0.86	1.44	.426
Axial pain	1.05	0.83	1.31	.699
Radicular pain	1.00	0.75	1.34	.986
Weakness	1.02	0.84	1.24	.865
Ambulatory preoperative	0.87	0.71	1.05	.150
Private insurance	0.79	0.65	0.97	**.023**
Previous spine surgery	1.08	0.89	1.31	.440
Number of levels				
1	Referent			
2	1.02	0.83	1.25	.884
3	0.84	0.64	1.12	.242
4 or more	1.41	1.06	1.88	**.019**
Ambulated same day as surgery	0.81	0.67	0.97	**.024**
Surgery length (h)	1.09	1.03	1.16	**.005**
Blood loss (cc)	1.00	0.99	1.01	.923
LOS (d)				
0-1	Referent			
2-3	1.02	0.71	1.47	.904
4+	1.16	0.79	1.71	.440
Discharged home	0.63	0.51	0.78	**<.001**

Bold values refers to statistical significance with $P<0.05$.

19%, and 18% decreased risk of readmission, respectively, for each of these factors.

Data on the number of patients requiring surgery after readmission were available for 914 of the 915 readmitted patients. Of these 914 patients, 385 (42.1%) required reoperation. The reasons for reoperation varied and the most frequently recorded was "other." The most common specified reasons for reoperation were infection (24.4%), hardware failure (13.5%), and pain (10.1%; Table 6).

DISCUSSION

Readmission after hospital discharge is expensive. Jencks et al[38] evaluated 11 855 702 Medicare beneficiaries and estimated the cost associated with readmission at $17.4 billion in 2004. In 2011, the cost was reported to be $41.3 billion based on 3.3 million readmissions.[39] Given the rising emphasis on cost containment in health care and the existence of financial penalty programs in Medicare for "excess readmissions," investigations into the incidence and factors contributing to readmission after spine surgery have become a high priority.[10,11,13]

To date, most studies have evaluated 30-d readmissions. In one investigation, Pugely et al[15] queried the NSQIP database to analyze 30-d readmission after lumbar spine surgery. A total of 15 668 patients were analyzed with an overall readmission rate of 4.4%. When excluding decompressive surgeries and evaluating just the 4361 patients who underwent posterior lumbar fusion, the rate was 5.4%. The most common causes for readmission were wound-related (38.6%), pain (22.4%), and thromboembolic (9.4%). Risk factors associated with increased risk for readmission were age, African American race, weight loss, chronic obstructive pulmonary disease (COPD), serum creatinine >1.2 mg/dL, ASA class 3 or 4, operative time >4 h, and hospital LOS >4 d. Garcia et al[17] also queried the NSQIP database to evaluate 30-d readmissions after single-level transforaminal lumbar interbody fusion. There was a 5.5% rate of readmission and the most common causes were deep (10%) and superficial (8.5%) SSI and pain

TABLE 6. Summary of Reasons for Reoperation Among Readmitted Patients[a]

Reason for return to OR	n (%)
Hematoma	34 (8.8%)
Cerebrospinal fluid leak	23 (6.0%)
Infection	94 (24.4%)
Wound dehiscence	37 (9.6%)
Revised implants	27 (7.0%)
Recurrent disc herniation	11 (2.9%)
Hardware failure	52 (13.5%)
Other	189 (49.1%)
Pain	39 (10.1%)

[a]More than one reason could be selected. Percentage represents the number of patients who returned to the OR out of the 385 patients who had a readmission.

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(8.5%). Regression analysis found that superficial SSI and urinary tract infection much more than COPD and ASA class were significant risk factors for readmission.

Beyond the 30-d window, assessment of the 90-d period can provide a more comprehensive view of the overall rate and factors associated with readmission. However, only a few studies have focused on 90-d readmissions. Utilizing a New York statewide administrative database, Baaj et al[23] evaluated 90-d readmissions in 86 869 patients who underwent lumbar fusion over a 10-yr period. A 24.8% rate of readmission was observed, and the most frequent reasons were neurological (3.8%), wound complications (3.7%), and wound infections (3.1%). Multivariate regression found a large number of potential risk factors for readmission, including age, sex, race, insurance, procedure type, number of fused levels, health service area, and multiple medical comorbidities. In one other recent study involving the neurosurgery Quality and Outcomes Database (QOD), 90-d readmissions for 9852 patients who underwent lumbar surgery were reported to be much lower at 6.3%.[40] Of the 9852 patients evaluated, only 3200 underwent fusion, which likely contributes to the wide difference in readmission rate. Another factor is that the QOD database is a prospective, spine-specific registry, which is likely more accurate than an administrative database. Regression analysis found that Medicare insurance, higher ASA class, and depression were risk factors associated with 90-d readmission.

In this study, the MSSIC registry was used to analyze 90-d readmissions. The MSSIC registry is similar to the QOD registry in that it is prospective, multicenter and spine-specific. Since the MSSIC registry is completely funded by BCBSM and BCN to provide administrative coordination, data abstraction and quality control at each participating institution, data accuracy is likely higher than administrative databases. In our analysis, the overall 90-d readmission rate was found to be 9.0%. This rate is higher than reported in the QOD study but is not necessarily inconsistent, since only fusion surgeries were analyzed in our study in contrast to the QOD investigation in which nonfusion surgeries were included.

With regard to reasons for readmission, the most commonly cited were "other" and "not related to previous noted complications," which are unfortunately nonspecific and reflect a deficiency in the original MSSIC registry design. Since an abstractor was allowed to select more than one cause, the "other" option could have been selected in addition to one of the listed reasons for readmission. The most specified reasons for readmission were pain, SSI, and radicular symptoms. Wound infection and, to a lesser extent, poorly controlled postoperative pain have been consistent findings in most investigations evaluating readmission. Both of these factors are potentially preventable and should be areas for further study.

One of the most impactful risk factors observed in this study was CAD, which was associated with a 57% higher risk for readmission compared to noncardiac patients. CAD has also been found to be an independent risk factor for readmission in otolaryngology patients and thought to be related to the physiological stress of surgery in patients with less cardiac reserve.[41] In addition to CAD, another comorbidity, diabetes, was found to be a risk factor for readmission. It is well known that diabetes can result in some degree of immunosuppression and thereby increase the likelihood of infection. Liu et al[42] studied 2715 patients undergoing lumbar surgery to evaluate risk factors for SSI and found that diabetes was the second most significant predictor for SSI, with an OR of 2.23. Interestingly, the most significant predictor for SSI found by Liu et al[42] was multilevel fusion, with an OR of 2.33. In this study, $\geq$4 levels fused was associated with a 41% higher risk for readmission compared to single level. This increased likelihood for SSI due to diabetes and $\geq$4 levels fused would be consistent with the most common specified reason for readmission being SSI in this study. In addition to diabetes and $\geq$4 levels fused, other race was found to have an 81% higher risk for readmission. The other race consisted of nonwhite and nonblack patients, and it is not easily discernable as to the nature of the increased risk. The other potential factor, surgery length, added only minimal relative increased risk.

In contrast to other studies evaluating readmission, multiple factors were found to decrease the risk of 90-d readmission. In concordance with the QOD study, private insurance was associated with a decreased likelihood of readmission. Although this may be due to a difference in financial status, it is unclear how specifically private insurance status would impact readmissions. Further investigation into insurance status is thus warranted. Similar to insurance, it is also not clearly evident as to why a diagnosis of spondylolisthesis was associated with an 18% decreased risk of readmission compared to a nonspondylolisthesis diagnosis. Discharged to home was found to have the largest decreased risk of readmission by 37%, which likely reflects less disability in the patient. This risk factor is also consistent with the causes of readmission, given that pain and radicular symptoms were common specified reasons for readmission, and those patients with severe postoperative pain or neurological

symptoms are more likely to be discharged to a sub-acute or acute facility. Early ambulation (ambulation on the day of surgery vs at some later time during the hospital stay) was associated with a 19% decreased likelihood for readmission. This is an important finding as it is a modifiable risk unlike most of the risk factors reported in other studies.

A significant number of readmitted patients (42.1%) required another surgery, with the most common specified reasons being infection, hardware failure, and pain. This is not a surprising finding given that SSI and pain were 2 of the most frequent causes for readmission. Unfortunately, details as to the pain etiologies that would require reoperation were not easily discernable. Notably, hardware failure as well as revision of implants was also commonly cited reasons for redo surgery. Instrumentation failure typically does not occur early and this relatively high frequency is likely a reflection of the longer 90-d period of evaluation.

Limitations

Even with dedicated abstractors at each participating institution, complete data collection was not achieved. Another potential issue is that readmission to an institution different from that in which the index surgery occurred could be missed within the MSSIC registry. However, this would likely be an infrequent occurrence.

CONCLUSION

Rehospitalization after lumbar fusion surgery is relatively frequent, with a 90-d readmission rate of 9.0%. Common reasons for readmission were pain, wound infection, and radicular symptoms. In particular, increased focus on postoperative pain management may decrease readmissions. Among potential risk factors associated with readmission, early postoperative ambulation is most easily modifiable. Comorbidities such as CAD and diabetes are conditions that should be optimized preoperatively and carefully managed in the perioperative and postoperative periods.

Disclosures

The MSSIC is funded by BCBSM and the BCN as part of their Value Partnerships program. Dr Schwalb is a consultant for Guidepoint, receives research funding from Medtronic and Salary support from Blue Cross Blue Shield of Michigan. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Park is a consultant to Globus, Medtronic, NuVasive, and Allosource and has received royalties from Globus. Dr Chang is a consultant for Globus, K2M, and SpineGuard, and has research relationships with Medtronic. Dr Oppenlander is a consultant for Globus. Dr Abdulhak is a consultant for Seaspine and Ulrich Medical.

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Koos Classification of Vestibular Schwannomas: A Reliability Study

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Received, April 4, 2018.
Accepted, August 1, 2018.
Published Online, August 30, 2018.

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BACKGROUND: The Koos classification of vestibular schwannomas is designed to stratify tumors based on extrameatal extension and compression of the brainstem. While this classification system is widely reported in the literature, to date no study has assessed its reliability.

OBJECTIVE: To assess the intra- and inter-rater reliability of the Koos classification system.

METHODS: After institutional review board approval was obtained, a cross-sectional group of the Magnetic Resonance imagings of 40 patients with vestibular schwannomas varying in size comprised the study sample. Four raters were selected to assign a Koos grade to 50 total scans. Inter- and intrarater reliability were calculated and reported using Fleiss' kappa, Kendall's W, and Intraclass correlation coefficient (ICC).

RESULTS: Inter-rater reliability was found to be substantial when measured using Fleiss' kappa (.71), extremely strong using Kendall's W (.92), and excellent as calculated by ICC (.88). Intrarater reliability was perfect for 3 out of 4 raters as assessed using weighted kappa, Kendall's W and ICC, with the intrarater agreement for the fourth rater measured as extremely high.

CONCLUSION: We have demonstrated that the Koos classification system for vestibular schwannoma is a reliable method for tumor classification. This study lends further support to the results of current literature using Koos grading system. Further studies are required to evaluate its validity and utility in counseling patients with regard to outcomes.

KEY WORDS: Koos reliability, Vestibular schwannoma

Neurosurgery 85:409–414, 2019 DOI:10.1093/neuros/nyy409 www.neurosurgery-online.com

Vestibular schwannomas are benign, slow growing tumors that originate in the internal auditory canal and extend into the cerebellopontine angle (CPA). These tumors represent 6% to 7% of all intracranial tumors and approximately 90% of all tumors occurring at the CPA. Bilateral lesions are associated with neurofibromatosis type-2 and show a highly variable growth rate along with a strong association with other tumors such as gliomas and meningiomas. Vestibular schwannomas present in the third to fifth decades of life with an annual incidence of 1 per 100 000.[1] Current management options include observation, radiation treatment, and surgical resection. Management strategies vary from center to center and depend on size, growth, and patient risk factors. The risk to adjacent structures, in particular hearing preservation and facial nerve function, is a critical component of patient counselling and selection of treatment modality, thus classification schemes have been proposed that stratify surgical risk and predict surgical outcome.[2]

Several studies have concluded that tumor size is the primary determinant when it comes to outcome of both hearing preservation and facial function.[1-4] The Koos classification of vestibular schwannomas, introduced in 1998, is one such system designed to stratify these tumors based on size including extrameatal extension and compression of the brainstem. Grade I tumors are completely confined to the internal auditory canal. Grade II tumors have both intra- and extrameatal components, but do not contact the brainstem. Grade III tumors make contact with

ABBREVIATIONS: CPA, cerebellopontine angle; **ICC,** intraclass correlation coefficient; **IRB,** Institutional review board; **MRI,** magnetic resonance imaging

the brainstem but do not compress it, while grade IV tumors cause brainstem compression.[3] While this classification system is widely reported in the literature, to date no study has assessed its reliability. In this study, we present an assessment of the intra- and inter-rater reliability of the Koos classification system.

METHODS

Data Collection and Rating

A cross sectional group of appropriate images from patients presenting within the past 3 yr with the diagnosis of vestibular schwannoma was assembled. Institutional review board (IRB) approval was obtained before patient data were accessed. Patient consent was not necessary as only patient's electronic medical records were accessed for which IRB approval suffices. Sample size was calculated based on an expected kappa coefficient of 0.6 and desired power of 0.8.[5] Imaging from 40 patients was selected with tumors of various size including intracanalicular only (10 patients), extension into the CPA without brainstem contact (10 patients), extension into the CPA with brainstem contact but no compression (10 patients), and extension into the CPA with brainstem compression (10 patients). Inclusion criteria included the presence of an intracanalicular mass with or without extension into the CPA. Exclusion criteria included patients with poor quality imaging. Magnetic resonance imaging (MRI) scans were organized into an anonymous database within the hospital's imaging system for easy viewing. Four raters were selected, including 1 attending neurosurgeon, 1 attending neuro-otologist, 1 neurosurgery resident, and 1 otolaryngology (ENT) resident. All raters were blinded to the patients' medical information. Each rater was asked to assign a Koos grade to a total of 50 MRI scans. A representative example of each grade is presented in Figure 1. Each scan included all orientations (axial, coronal, and sagittal) and a variety of sequences including standard T1, T2, and T1 postcontrast sequences as well as skull base focused series such as Driven equilibrium or Fast Imaging Employing Steady-state acquisition allowing for increased visualization of cranial nerves and vessels. The smallest slice thickness of the images used was .6 mm. All of the ratings were conducted independently, and all of the images were of good quality and contained orthogonal views. Ten randomly chosen patient scans were evaluated twice by each rater to measure intrarater reliability. Additionally, each rater was provided a handout explaining the Koos grading system with images and definitions (Figure 2). The manuscript was prepared following the Guidelines for Reporting Reliability and Agreement Studies.[6]

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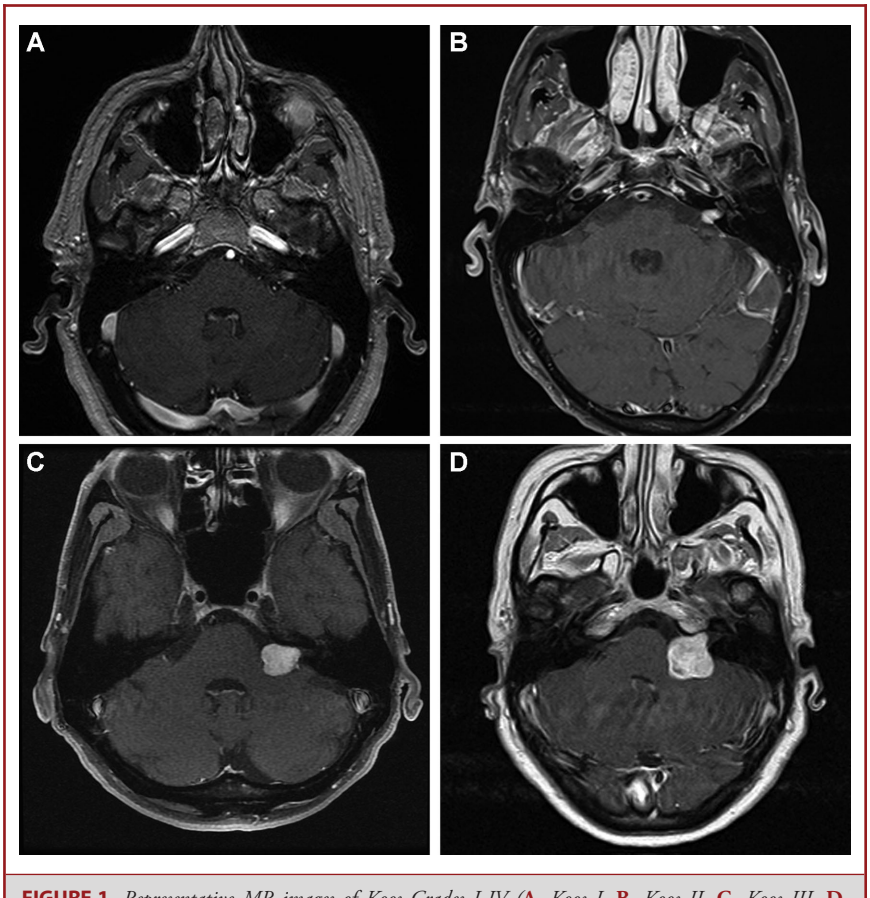


FIGURE 1. *Representative MR images of Koos Grades I-IV (A, Koos I, B, Koos II, C, Koos III, D, Koos IV).*

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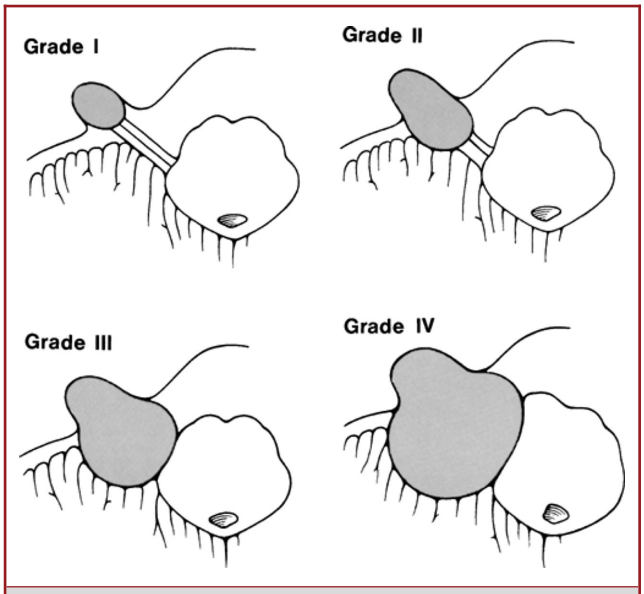


FIGURE 2. *Koos Grading System as described by Wolfgang T. Koos. Grade I = small intracanalicular tumor. Grade II = small tumor with protrusion into the CPA; no contact with the brainstem. Grade III = tumor occupying the cerebellopontine cistern with no brainstem displacement. Grade IV = large tumor with brainstem and cranial nerve displacement. Republished with permission by JNSPG from Koos et al.*[12]

Statistical Analysis

Inter-rater reliability was computed using Fleiss' generalized kappa for multiple raters, Kendall's coefficient of concordance (W) and intra-class correlation coefficient (ICC). Intrarater reliability, also known as test-retest reliability, was assessed using weighted kappa with quadratic (Fleiss–Cohen) weights.

Fleiss' generalized kappa is a revision of Cohen's kappa and is used to measure inter-rater reliability among three or more raters. Agreement measured by kappa is widely considered as almost perfect with kappa coefficients between .81 and 1.00. A kappa coefficient between .61 and .80 is viewed as substantial, a coefficient between .41 and .60 is considered moderate, a coefficient between .21and .40 is interpreted as only fair, and a coefficient less than .21 is viewed as poor.[7,8]

Data were also analyzed using the lesser known Kendall's coefficient of concordance. This is a nonparametric test popular for ordinal categories and is a test of concordance that quantifies agreement of rankings of the ratings. A coefficient between .71 and .90 is considered as extremely strong agreement, a coefficient between .51 and .70 is classified as strong agreement, a coefficient between .31 and .50 is interpreted as moderate agreement, and weak agreement is classified as a coefficient between .11 and .30.[9]

ICC is a widely-used reliability index for quantitative data that compares the variability of multiple raters rating the same scans to the total variation across all ratings and all scans.

Since this study design assumed a 2-way random effects model and used 4 raters who each rated all patients' scans, the Shrout and Fleiss ICC Model 2 ($ICC_{2,1}$) was employed to analyze absolute agreement. Based on Fleiss' interpretation of the ICC, a value greater than .75 is indicative of excellent inter-rater reliability, an ICC between .40 and .75 is interpreted as fair to good, and less than .40 is considered poor agreement.[7]

Useful for assessing intrarater agreement, weighted kappa is typically used for 2 raters rating categorical data on an ordinal scale such as found in the Koos classification system. As proposed by Cohen, weighted kappa gives different weights according to the magnitude of the degree of disagreement between ratings.[10] Weighted kappa can be interpreted similarly to Fleiss' kappa.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) and SPSS version 25 (IBM Inc, Armonk, New York). The SAS MAGREE macro version 1.0 was used to calculate Fleiss' generalized kappa for multiple raters and Kendall's coefficient of concordance while ICCs were performed using SPSS.[11] A *P*-value less than .05 was considered statistically significant. The *P*-values in Tables 1 and 2 express the probability of obtaining the specific inter-rater reliability coefficient (kappa, Kendall's W, or ICC) as large as or larger than what is computed given that the null hypothesis (ie, the agreement among raters is due to chance) is true. Lower *P*-values provide stronger evidence against the null hypothesis that the agreement among raters is due to chance.

RESULTS

The results listed below were based off a total of 4 raters (attending neurosurgeon, attending neuro-otologist, resident neurosurgeon, and resident ENT) and 50 total images. Ten of these images were replicates used for test-retest reliability.

Inter-rater Reliability

The level of observer agreement was similar as determined by the 3 methods used to calculate inter-rater reliability in this study. Inter-rater observer reliability was found to be substantial when measured using Fleiss' kappa (.71), extremely strong using Kendall's W (.92), and excellent as calculated by ICC (.88). The results were all statistically significant and are listed in Table 1.

Intrarater Reliability

The assessment of observer agreement included intrarater reliability, and agreement for the individual raters is shown in Table 2. Intrarater reliability for Koos grade was perfect for 3 out of 4 raters as assessed using weighted kappa, Kendall's W and ICC, with the intrarater agreement for the fourth rater measured as extremely high reliability. This rater was the ENT resident. The results were all statistically significant and are listed in Table 2.

DISCUSSION

Throughout the literature, vestibular schwannomas are widely characterized by their size, volume, or extrameatal extension on imaging. The methods by which size and volume are calculated vary and are inevitably subject to human error. One of the more common and widely established grading systems used is the Koos classification.[12] The Koos classification system, developed by Wolfgang T. Koos and colleagues, is designed to grade these tumors based on radiographic features, specifically

TABLE 1. Koos Grading Scale—Inter-rater Reliability Estimates, n = 40

Parameter	Kappa (κ)	SE	*P* value	Kendall's W coefficient	*P* value	Intraclass coefficient (ICC)	*P* value
Tumor grade	.71	.04	<.001*	.92	<.001*	.88	<.001*

κ, Fleiss' generalized Kappa for multiple raters; Kendall's coefficient of concordance (W) for ordinal data; intraclass correlation (ICC) for ordered, Likert-type, or continuous data. SE, standard error;
**P* value < .05 considered statistically significant.

TABLE 2. Koos Grading Scale - Intra-rater Reliability Estimates of Tumor Grade, n = 40

	Kappa (κ)	ASE	*P* value	Kendall's W coefficient	*P* value	Intraclass coefficient (ICC)	*P* value
Rater 1	1.00	0	<.001	1	<.001*	1	–
Rater 2	1.00	0	<.001	1	<.001*	1	–
Rater 3	.92	.07	<.001	.99	<.001*	.96	<.001*
Rater 4	1.00	0	<.001	1	<.001*	1	–

Weighted kappa (quadratic weights); Kendall's coefficient of concordance (W) for ordinal data; intraclass correlation (ICC) for ordered, Likert-type, or continuous data. ASE, asymptotic standard error;
**P* value < .05 considered statistically significant.

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extrameatal extension and contact or compression of the brainstem. The Hannover grading system, first described in 1997, also classifies tumors according to their extrameatal extension but in greater detail. Tumors are either T1 (purely intrameatal), T2 (intraextrameatal), T3a (filling the cerebellopontine cistern), T3b (reaching the brainstem), T4a (compressing the brainstem), or T4b (severely dislocating the brain stem and compressing the fourth ventricle).[13] To date, the authors are unware of any study assessing the reliability or validity of either of these grading systems despite widespread usage.

We present our results of a reliability study of the Koos grading system. The level of interrater reliability was substantial based on a Fleiss' kappa, extremely strong based on a Kendall's W and excellent based on a calculated ICC. Intrarater reliability was perfect for three and extremely high for one 1 of the 4 raters. Taken all together, these results confirm that the Koos classification system is a significantly reliable and feasible means to characterize these tumors.

Interestingly, studies continue to be performed incorporating the Koos classification system despite the absence of any formal reliability assessment. These studies, discussed below, are heavily focused on determining the best treatment of these tumors based on a variety of factors, including Koos grade. Although a relatively simple grading scheme, it remains subject to human interpretation. The reliability of every outcome measure, especially those requiring human interpretation must be established before they are correlated to patient outcomes and treatment efficacy.

A recent meta-analysis found facial nerve preservation in 96% and serviceable hearing preservation in 59.9% of patients with Koos grade IV (or >3 cm) tumors treated with subtotal resection followed by SRS.[14] A study in 2013 correlated the Koos grades with tumor volumes and assessed outcomes after radiosurgery.[4] They found that within each Koos grade, volumes varied widely. In addition, the tumor volumes doubled or tripled with each increase in grade. They found no significant correlation with outcomes after radiosurgery. Additionally, isodose lines for patients undergoing SRS are being adapted based on their Koos grade. A recent published protocol prescribed doses targeting the 70% isodose line for grade I, 60% to 70% isodose line for grade II and 50% isodose line for grade III or IV.[14] This treatment strategy, in addition to the development of the Gamma Knife Perfexion unit (Elekta AB, Stockholm, Sweden) in 2012 has led to a significant reduction in complication rates after radiosurgery. One of the biggest limitations of these studies was that they were assessing the validity of a grading system that had not yet been proven reliable. The studies cited above are only a small subset of the relevant literature. Our results provide further support for all current literature incorporating Koos into their methods, especially those correlating it with outcomes.

Conversations with the patient regarding treatment options are important when it comes to counseling and prognostication. Now that the reliability of this system has been demonstrated, further studies assessing validity are warranted. We are currently working on a retrospective study correlating Koos grade to outcomes after microsurgery, radiosurgery, or both. The results of this study will hopefully aid in the counseling of patients and facilitate conversations regarding treatment options and prognosis by using a uniform, reliable and valid classification system.

CONCLUSION

We have demonstrated that the Koos classification system for vestibular schwannoma is a significantly reliable and feasible means to characterize these tumors. This study lends further support to the results of current literature using Koos grading system. Further studies are required to evaluate its validity and utility in counseling patients with regard to outcomes.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

This is a nice, neat, well-constructed study which confirms the inter- and intraobserver reliability in assigning a Koos class to patients with an acoustic neuroma. As the authors point out there is a wide variability in the actual tumor volumes within a grade. Whether this has more of an impact on patient outcome than the grade itself will require well-constructed studies of the validity of this grading system in predicting outcome and thus on its prognostic value.

Franco DeMonte
Houston, Texas

For treating physicians to report their results from any particular intervention it would be optimal if it was clear what the treated population looked like exactly, to make comparison between series practical. The Koos classification of vestibular schwannomas helps somewhat in that regard. It is fairly easy to remember and has been in practice long enough that it is rather internationally well known. This study proves that it is also reliable among different observers with different levels of experience. Therefore, for instance, a reader can feel very confident a series reporting results from microsurgical resection of Koos grade 1 and 2 tumors contains no tumor that contacts the brainstem.

Admittedly, we have never used the Koos system. The categories are too broad, in my opinion, to provide practical information regarding prognosis from treatment. For example, even intracanalicular Koos grade 1 tumors represent a heterogeneous group. A tumor impacted in the distal internal auditory canal, below the transverse crest, has different treatment ramifications compared to a tumor at the porous with a large fundal cap of cerebrospinal fluid. We prefer to report tumor size from our surgical series based on the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Committee reporting guidelines.[1] Tumor size is estimated as the square root of the product of the maximal transverse and anteroposterior diameters of the tumor. Ideally, tumors should be reported based on volumetric analysis as is easily done in radiosurgery series, in which the software provides a precise report of tumor size down to the cubic millimeter.

Much like the Glasgow coma scale (in which a patient gets 3 points just for showing up), the Hunt-Hess subarachnoid hemorrhage score, or the House-Brackmann facial nerve grading scale, there are shortcomings in any grading system. It is reassuring however, to know that when someone refers to a Koos grade tumor it is a reliable report of tumor size within that classification system.

Michael J. Link
Rochester, Minnesota

1. American Academy of Otolaryngology-Head and Neck Surgery Foundation. Committee on Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma). Otolaryngol Head Neck Surg. 1995;113(3):179-180.

The authors are to be commended for adding to the neurosurgical literature this necessary, although not exciting, work in demonstrating the reliability of the Koos grading system for vestibular schwannoma. If physicians followed a logical order of development of such rating scales, one of the first evaluations done when a new scale was developed would be a study of the intra- and interrater reliability (reproducibility) of the scale. A scale is a measurement tool and a measurement tool that gives inconsistent results when repeated measurements are made by the same user is not useful. Similarly, even if it is consistent for a single user, if measurements under identical conditions give unreasonably different results depending on the user, the tool is of little value.

Despite this logic, it is not unusual to find in the neurosurgical literature examples of newly developed scales recommended for widespread adoption without any evidence to support their reliability. Before adopting new scales or other assessment tools, neurosurgeons should require evidence of reliability. Therefore, although reliability research is unlikely to lead to Nobel prizes, it is a necessary early step in high-quality clinical research and provides information essential to the proper use of clinical evaluation tools. This article provides that information for the

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Koos grading scale and also presents a good example of how such research should be done and reported.

Stephen J. Haines
Minneapolis, Minnesota

A cross-sectional group of the MRIs of 40 patients (50 scans) with acoustic schwannomas confirmed were analyzed by 4 raters, then inter- and intra-rater reliability were calculated. The authors found that the Koos classification system is reliable method for acoustic schwannomas classification. It is a very interesting article that reaffirmed and validated previous knowledge.

J. Manuel Revuelta Barbero
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Fascicular Ratio Pilot Study: High-Resolution Neurosonography—A Possible Tool for Quantitative Assessment of Traumatic Peripheral Nerve Lesions Before and After Nerve Surgery

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Received, January 22, 2018.
Accepted, July 11, 2018.
Published Online, August 9, 2018.

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BACKGROUND: Clinical and electrophysiological assessments prevail in evaluation of traumatic nerve lesions and their regeneration following nerve surgery in humans. Recently, high-resolution neurosonography (HRNS) and magnetic resonance neurography have gained significant importance in peripheral nerve imaging. The use of the grey-scale-based "fascicular ratio" (FR) was established using both modalities allowing for quantitative assessment.

OBJECTIVE: To find out whether FR using HRNS can assess nerve trauma and structural reorganization in correlation to postoperative clinical development.

METHODS: Retrospectively, 16 patients with operated traumatic peripheral nerve lesions were included. The control group consisted of 6 healthy volunteers. All imaging was performed with a 15 to 6 MHz ultrasound probe (SonoSite X-Porte; Fujifilm, Tokyo, Japan). FR was calculated using Fiji (𦛚) on 8-bit-images ("MaxEntropy" using "Auto-Threshold" plug-in).

RESULTS: Thirteen of 16 patients required autologous nerve grafting and 3 of 16 extra-intraneural neurolysis. There was no statistical difference between the FR of nonaffected patients' nerve portion with 43.48% and controls with FR 48.12%. The neuromatous nerve portion in grafted patients differed significantly with 85.05%. Postoperatively, FR values returned to normal with a mean of 39.33%. In the neurolyzed patients, FR in the affected portion was 78.54%. After neurolysis, FR returned to healthy values (50.79%). Ten of 16 patients showed clinical reinnervation.

CONCLUSION: To our best knowledge, this is the first description of FR using HRNS for quantitative assessment of nerve damage and postoperative structural reorganization. Our results show a significant difference in healthy vs lesioned nerves and a change in recovering nerve portions towards a more "physiological" ratio. Further evaluation in larger patient groups is required.

KEY WORDS: High-resolution neurosonography, Traumatic nerve lesion, Fascicular ratio

Neurosurgery 85:415–422, 2019 DOI:10.1093/neuros/nyy355 www.neurosurgery-online.com

Recently, imaging of traumatic nerve lesions has improved significantly, and hence has influenced decision-making in surgical management. This accounts for both magnetic resonance imaging (MRI) (MR-neurography, MRN) and ultrasound (high-resolution neurosonography, HRNS).[1-3] Especially in the preoperative stage, in absence of clinical or electrophysiological reinnervation signs, these techniques facilitate correct localization and assessment of the depth of nerve damage. As an easy to use and pervasive tool, HRNS has even been introduced to the intraoperative setting.[4]

ABBREVIATIONS: FR, fascicular ratio; **HRNS,** high-resolution neurosonography; **MRI,** magnetic resonance imaging; **MRN,** MR-neurography; **NAP,** nerve action potential; **ROI,** region of interest

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Taking imaging from a purely descriptive level to quantitative assessment, Boom and Visser (2012)[5] and Tagliafico et al (2016)[6] used both MRN and HRNS to establish the so-called fascicular ratio (FR) or nerve density to discern healthy nerves from inflammatory, tumorous, or compression neuropathies. The ratio is based on the observation that the axon- and myelin-bearing normal endoneurium, which forms the fascicles, appears hypoechogenic on HRNS and hypointense on MRN, respectively. In contrast, the connective tissue between the fascicles appears hyperechogenic in HRNS due to a lower content of water.[7] The ratio of fascicular to nonfascicular structures can be used for quantification of nerve lesions with typical changes in different pathologies.[8] But, it has to be kept in mind that FR reflects imaging characteristics only and does not depict the actual number of axons within the distinct nerve portion.

In traumatic peripheral nerve lesions, numerous descriptions of morphological changes have been published.[9,10] However, the role of HRNS as a quantitative tool in imaging of traumatic damaged nerves and the postoperative alterations remains widely unexplored. Quantitative assessment of operated nerves in the postoperative phase after peripheral nerve trauma in patients and the correlation to clinical outcome has not been published yet (www.pubmed.com; 28.11.2017, 10:41 am). Usually, postoperative evaluation is done by clinical and electrophysiological assessment. Reliable and easy to use imaging is still lacking.

Basically, we tracked sonomorphological alterations by HRNS in the postoperative phase and analyzed the FR. Our intention was to evaluate the potential capacity of this parameter to discern damaged from normal or even recovering nerve. In the next step, we correlated the obtained images with the clinical course, thus validating the possible role of HRNS for the assessment of a nerve's regenerative potential.

To our knowledge, this is the first description of the FR as a quantitative assessment of postoperative structural changes in traumatic peripheral nerve lesions before and after surgery against healthy controls in correlation to the clinical results obtained.

METHODS

Patients

In 2015 to 2016, a total of n = 103 patients with traumatic nerve lesions were operated at our department. Of these, we included n = 16 patients and retrospectively reviewed medical charts and HRNS imaging.

All patients were screened using HRNS with a 15 to 6 MHz ultrasound probe (SonoSite X-Porte; FujiFilm Inc, Tokyo, Japan). All neurosonography was done by an experienced neurosurgeon and neurosonologist.

Preoperatively, the healthy portion of the affected nerve proximal to the lesion as well as the portion affected the most by neuromatous changes was assessed in transverse views. At follow-up, the proximal suture- and neurolysis sites were depicted, respectively. All patients have given their written informed consent and the study was approved by the local ethics committee.

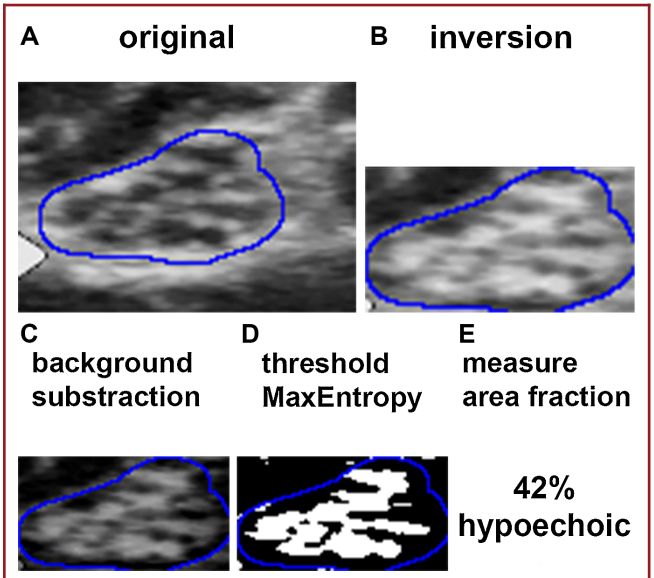


FIGURE 1. *Example of image processing.* **A**, *original ultrasound image.* **B**, *image after inversion.* **C**, *image after background subtraction.* **D**, *image after application of MaxEntropy threshold.* **E**, *resulting FR after measuring hypoechoic area fraction in % (FR, fascicular ratio calculated in %).*

Controls

N = 6 healthy controls were enrolled, n = 3 of them female, n = 3 male, with a mean age of 35.3 yr. In all controls, there was no clinical evidence of peripheral neuropathy. Both ulnar and median nerves were scanned in the left and right forearm in transverse view. Multiple images were acquired. In addition, images were taken at defined spots at several points of time within the same session and after 8 mo.

Image Analysis

The freely available program Fiji[11] was used for processing and analyzing the sonographic images. All sonographies were converted to 8-bit images with 256 shades of grey (0 = pure black; 255 pure white). The region of interest (ROI) was manually set and verified by 2 experienced neurosurgeons/neurosonologists. For an enhancement of contrast, the images were inverted and subjected to background subtraction using a rolling ball radius of 30 to 100 pixels depending on the image resolution. Within the ROI, hypoechogenic areas were selected based on the "MaxEntropy" method using the "Auto-Threshold" plug-in,[12,13] which provides a quantitative assessment of the echogenicity to discriminate normal and pathological peripheral nerves.[5] The hypoechogenic fraction was calculated using the "Measure area fraction" function (see Figure 1A-1E processing).

Statistical Analysis

For comparison of the normally distributed variables, 1-way ANOVA with a Bonferroni multicomparison test was used. The level of significance was set at a *P*-value of $P \leq .05$ (*), $P \leq .01$ (**), and $P \leq .001$ (***) for all analyses.

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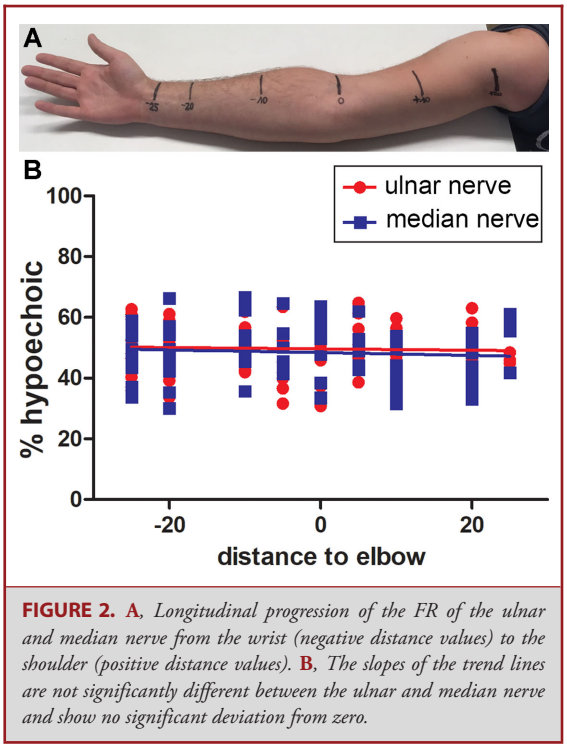


FIGURE 2. **A**, *Longitudinal progression of the FR of the ulnar and median nerve from the wrist (negative distance values) to the shoulder (positive distance values).* **B**, *The slopes of the trend lines are not significantly different between the ulnar and median nerve and show no significant deviation from zero.*

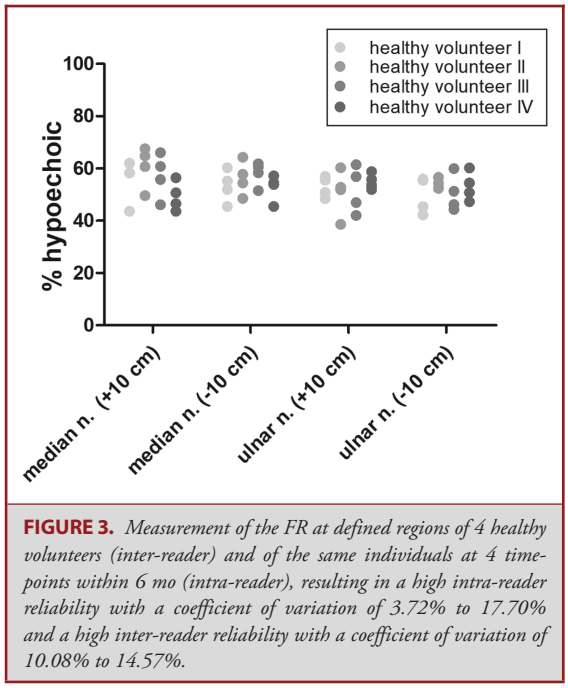


FIGURE 3. *Measurement of the FR at defined regions of 4 healthy volunteers (inter-reader) and of the same individuals at 4 time-points within 6 mo (intra-reader), resulting in a high intra-reader reliability with a coefficient of variation of 3.72% to 17.70% and a high inter-reader reliability with a coefficient of variation of 10.08% to 14.57%.*

RESULTS

Controls

N = 6 healthy controls were included, of these n = 3 were female, n = 3 were male. The mean age was 35.3 yr. To ensure a constant FR along the entire length of the nerves, the FR was measured at defined sites of the median and ulnar nerve (see Figure 2A) of n = 4 healthy volunteers (Figure 2B). The slope of linear trendlines showed neither significant differences between the median and ulnar nerve, nor significant deviations from zero, ensuring a comparable and constant FR along the entire length of the median and ulnar nerves. To prove reliability, the FR of the ulnar and median nerves were also measured over time (at defined points, in independent sessions carried out within 8 mo) in 4 healthy volunteers, resulting in a high reproducibility of data within the same individual (Figure 3, coefficient of variation: range 3.72%-17.70%; mean 11.58%; intrareader analysis) as well as different individuals (Figure 3, coefficient of variation: range 10.08%-14.57%; mean 11.78%; inter-reader analysis).

Patients

N = 16 consecutive patients were included in this preliminary study. N = 2 were female, n = 14 were male, the mean age at surgery was 40.25 yr (range 18-68 yr). The following nerves were involved: n = 6 radial nerves, n = 5 peroneal nerves, n = 2 posterior interosseous nerves, n = 1 accessory nerve, n = 1 ulnar, and n = 1 musculocutaneous nerve. Mean time from trauma to nerve surgery was 7.25 mo (range 4-17 mo), mean follow-up was 9.9 mo (range 4-23 mo). All patients had a complete preoperative sensorimotor function loss of the affected nerve. N = 13 patients required nerve grafting with a mean graft length of 9.5 cm (range 2-17 cm), while in n = 3 patients an extra-intraneural neurolysis was performed (for clinical data see Table 1).

All surgeries were performed by the authors using a microscope, nerve stimulation, intraoperative nerve action potential (NAP)/electromyography, and HRNS. Decision for either grafting or neurolysis was based on the lesion type, applying principles of intraoperative assessment based on the combination of Sunderland/Millesi lesion classification, NAP recording according to Kline, and intraoperative neurosonography.[14-17]

N = 1 patient was lost to follow-up. In n = 13/16 patients (n = 10 grafted/n = 3 neurolyzed), postoperative HRNS was available (see Table 2).

Statistical analysis of the HRNS images revealed no significant difference between nonaffected grafted patients' nerve portion with an FR value (mean) of 43.48% and the healthy controls (see Figure 4) with an FR value of 48.12% (see Figures 4E and 4F and 5).

In contrast, as revealed by preoperative HRNS, the neuromatous nerve portion differed significantly from healthy controls' and patients' unaffected nerve portion (see Figure 4) with an FR value of 85.05% in grafted and 78.54% in neurolyzed patients, respectively (see Figures 4A, 4C, 4E, and 4F and 5).

Following nerve grafting, FR values returned to more "physiological" values with a mean FR of 37.66% (see Figure 4), not statistically different from healthy controls and healthy nerve portions in patients (see Figures 4B, 4E, and 4F and 5).

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TABLE 1. Clinical Data

Patient	Age at surgery	Affected nerve	Time trauma-OP (mo)	Follow-up (mo)	Graft length (cm)
1	24	ulnar	6	23	2
2	18	peroneal	8	21	15
3	41	musculocutanaeous	4	10	15
4	40	posterior interosseous	5	8	4
5	27	peroneal	5	12	15
6	55	radial	14	4	4
7	42	accessory	17	12	6
8	62	radial	4	5	11
9	53	posterior interosseous	4	6	5
10	59	radial	3	7	6
11	20	peroneal	10	5	17
12	22	peroneal	5	6	14
13	52	radial	4	not available	5
14	68	radial	5	13	neurolysis
15	39	peroneal	17	11	neurolysis
16	22	radial	5	6	neurolysis

TABLE 2. Results of Imaging and Clinical Development

Patient	Preop hrns correct identification damaged/intact nerve	Clinical/ electrophysiological reinnervation	Postop hrns with normalization
1	yes	yes	yes
2	yes	yes	yes
3	yes	yes	yes
4	yes	yes	not available
5	yes	no	yes
6	yes	yes	yes
7	yes	yes	yes
8	yes	no	yes
9	yes	yes	yes
10	yes	yes	yes
11	yes	no	not available
12	yes	no	yes
13	yes	not available	not available
14	yes	yes	yes
15	yes	no	yes
16	yes	yes	yes

Hrns, high-resolution neurosonography

At the degenerated end located distal to the grafting-site, preliminary data of one patient showed normal FR values (pre-OP) with a mean FR of 51.63% (Figure 6A-6E).

In the neurolysis patients, post-OP mean FR values of 50.79% were calculated, also pointing to a reduction of FR values towards more normal levels, comparable to healthy controls (mean FR value 48.12%), and healthy nerve portions of patients (see Figure 4) with a mean FR value of 43.48% (see Figures 4D, 4E, and 4F and 5).

In accordance with the HRNS data (more normalized FR values), n = 10/15 patients (grafted patients n = 8/neurolyzed patients n = 2) showed clinical and electrophysiological reinnervation, respectively. So far, in n = 4 patients, no signs of clinical and/or electrophysiological reinnervation are detectable.

However, postoperative FR in both sutured and neurolyzed nerve portion returned close to normal in all patients.

In contrast, changes in FR from pathological to healthy values correlated to postoperative clinical and/or electrophysiological reinnervation in 71.4%.

DISCUSSION

To our knowledge, this is the first study determining FR values in traumatic nerve lesions before and after nerve surgery.

Imaging has become an important and influential tool in the treatment of traumatic peripheral nerve lesions. Treatment decisions previously based on clinical assessment and electrophysiology can now be supported and frequently even secured by MRN and HRNS.[18] Overall, these tools substantially reduce the number of cases that are preoperatively left for observation, because of unclear regenerative potential.

The implementation of HRNS allows for detection of substantial nonregenerative nerve lesions requiring surgery much earlier (eg, transected nerves or nerves with massive scaring and/or neuroma). Thus, HRNS can contribute to obtain a better clinical outcome. Imaging has become an important noninvasive diagnostic tool to depict the severity of a lesion and to estimate the regenerative chance of a lesioned nerve.[3] As timing is crucial "time is muscle", such early acquired information influences the choice of optimal therapy and has therefore an impact on patient's functional outcome.[19]

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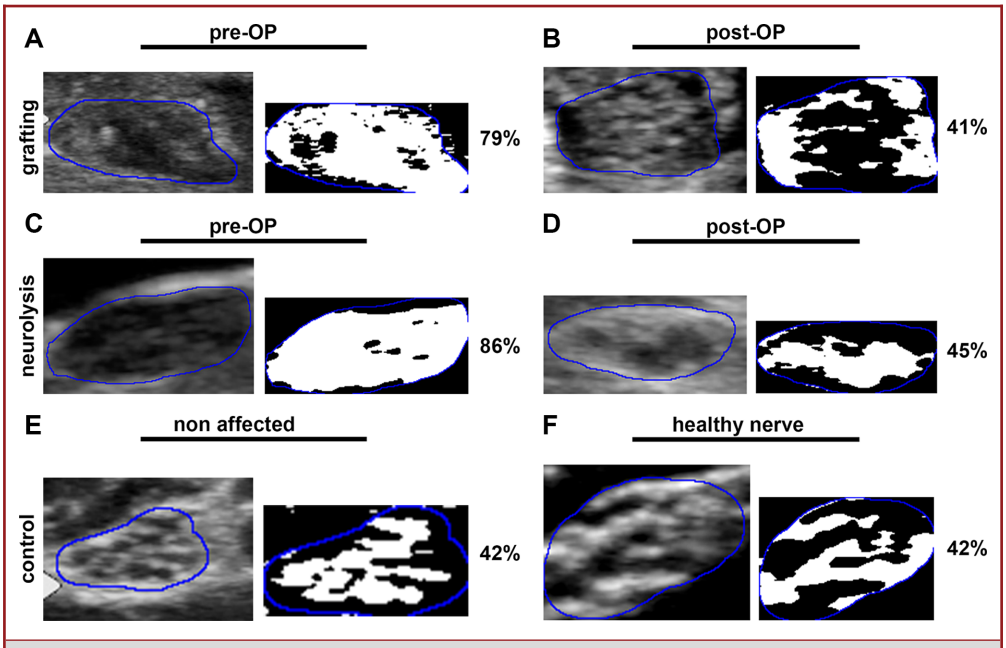


FIGURE 4. *Examples for calculation of FR.* **A**, *FR in the preoperative neuromatous nerve portion.* **B**, *FR in the postoperative regenerating grafted nerve portion.* **C**, *FR in preoperative neuromatous nerve portion.* **D**, *FR in the postoperative regenerating neurolyzed nerve portion.* **E**, *FR in the patient's nonaffected nerve portion.* **F**, *FR in healthy control's nerve.*

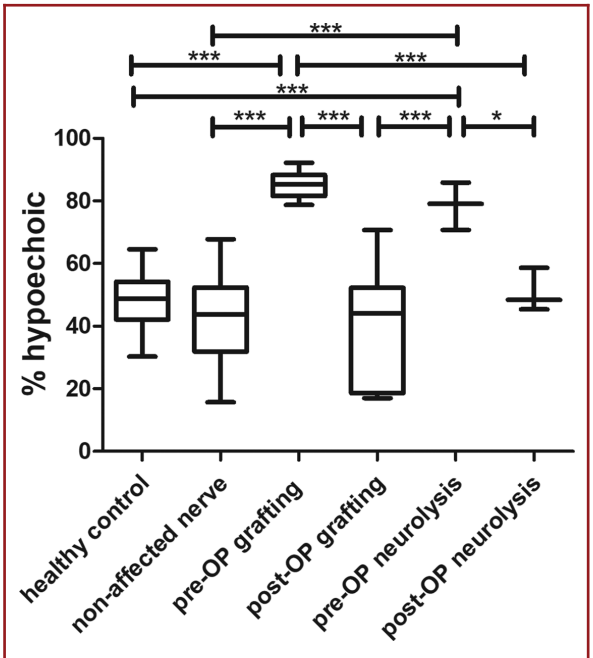


FIGURE 5. *Statistical FR analysis showing a significant deviation of pre-OP grafting and neurolysis FR-values compared to the respective post-OP FR. Post-OP FR-values returned to control FR (P ≤ .05 (*), P ≤ .01 (**), P ≤ .001 (***)).*

By improving and modifying a purely descriptive approach of imaging, the term "nerve density" or "fascicular ratio" was introduced to quantify nerve alterations using a 3T MR.[20] "Fascicular ratio" stands for the ratio of the hypoisointense fascicles and the hyperisointense intraneural connective tissue. As stated, FR does not assess the actual number of axons within the distinct nerve portion. It is just a grey-scale-based ratio of the individual imaging modality.

Different authors, mainly the working groups of Tagliafico et al (2016)[6] and Boom and Visser (2012),[5] have been reporting on its application in nerve compression syndromes, inflammatory neuropathies, and nerve tumors applying both imaging techniques, MRI and ultrasound.

Their findings suggest that FR values not only allow us to differentiate between healthy and affected nerves, but may also distinguish between the underlying pathologies.[5,8]

To this day, there are only a few studies that quantify structural changes correlated to tissue regeneration by means of ultrasound. There is no literature dealing with FR in nerve trauma and postoperative nerve imaging in patients. Hattori et al (2003)[21] described the feasibility of this method in documenting cartilage regeneration by comparing ultrasound ratio calculations with histology in an animal model.

In a "crush lesion" rabbit model, de Kool et al (2005)[22] assessed changes in ultrasound and compared the imaging data to histopathological results and electrophysiology received from the same nerves in a distinct course of time. However, in contrast

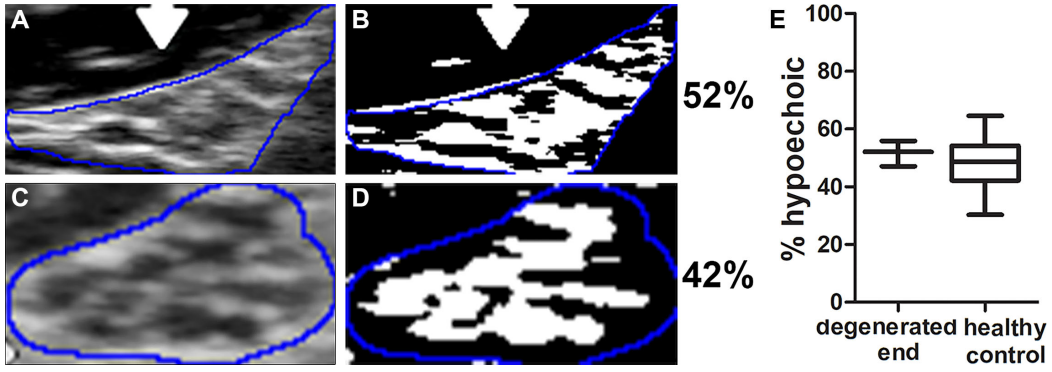


FIGURE 6. *Preliminary data: The FRs measured at the degenerated end of one patient (located distal to the grafting site; three measurements at different sites,* **A**, **B**, *and* **E**) *show normal FR values compared to the healthy volunteers (***C**, **D**, *and* **E**).

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to our approach, the authors calculated a mean grey-scale only without assessing an FR; thus, differentiation between hypo- and hyperechogenic parts was not performed. They concluded that the mean grey-scale did not correlate with electrophysiology and histopathology.[22]

In contrast to this animal study, the results of our study performed in humans clearly show that FR allows for reproducible and reliable differentiation between healthy and traumatically damaged nerve segments. This accounts for portions within the same nerve, as well as for different nerves in the same individual, and in comparison to controls.

Therefore, our results could give a positive answer to one of our main questions, whether FR facilitates differentiation of structurally intact and damaged nerve portions.

In addition, we could observe a significant change of pathological FR back to more "physiological" FR values in the course of time and ongoing clinical recovery in n = 12/16 patients. This could be due to regeneration processes that include depletion of scarred and damaged tissue and the regrowth and fascicular reorganization in the affected nerve's portion.[23] Assuming a more physiological internal microanatomical structure might be reflected in a more physiological appearance in HRNS and thus FR.

One critical aspect of this method is that ultrasound is extremely dependent on experience and individual examination regimes. Consequently, all HRNS measurements and most of the surgery presented in this study were done by the senior authors. This fact and a rather small patient sample might be a source of bias. However, our calculated mean FR values of a healthy nerve in both patients and controls subjects are in accordance with literature.[24]

Not all patients with a post-OP tendency towards normal FR values (positive changes in ultrasonic imaging) also showed clinical signs of reinnervation.

One reason could be delayed surgery after trauma that led to significant changes in the affected muscles. In this case, regeneration might be limited to the nerve itself. However, regain of muscular function may not take place due to loss of neuromuscular junctions resulting in fatty muscle conversion and therefore loss of the motor end organ. This might result in more physiological FR values despite persisting loss of function.[25]

Moreover, n = 3/4 patients without clinical recovery had a peroneal nerve lesion. This nerve is known to have one of the worst regeneration and recovery potentials of all nerves.[26] The fourth patient was a 62 yr-old radial nerve patient with severe renal problems. This may have impeded clinical recovery as well.

In addition, the grafted patients lacking clinical recovery were all supplied with long grafts, ranging from 11to 17 cm and the follow-up period was rather short with a mean of 7.3 mo (for the patients with absent clinical recovery). This might explain that the observed positive changes in the sonographic images (FR values) were already visible at the suture site, but that the regenerating nerve may not have reached its muscles (yet).

The quantitative assessment of nerve echogenicity in HRNS was carried out using the scientific image-analysis program Fiji.[11] All sonographs were analyzed according to an automated-threshold protocol published by Boom and Visser (2012),[5] generating a binary image of the hyper- and hypoechogenic nerve areas. As a high contrast of hyper- and hypoechogenic nerve fraction is crucial for threshold-based quantification, a background subtraction step was additionally introduced for contrast enhancement prior to the thresholding procedure. Hypoechogenic nerve fractions were selected by automatic thresholding based on the "MaxEntropy" method, which was recommended by Boom and Visser (2012).[5] In order to gain comparable and reproducible results, (a) the brightness and contrast, (b) the imaging angle (transverse), and (c) the minimum resolution need to be constant (in a comparable range) for all raw-sonographies. These are prerequisites for useful assessment, especially when HRNS is performed by different neurosonologists without a standardized imaging-protocol. Moreover, manual ROI selection,

which requires a trained neurosonologist, can be a source of bias as well, while all subsequent steps can be automated and/or performed by non-neurosonologists.

Evaluation of nerve recovery remains a domain of clinical and electrophysiological diagnostics. But a reliable imaging method to assess quality and quantity of nerve regeneration is still missing. Our observations suggest that the use of FR in HRNS could be a useful enhancement in nerve injury assessment as an additional screening tool, and especially for monitoring of the ongoing restructuring during the regenerative process. A differentiation between healthy and traumatically damaged nerve portions was feasible in all our patients indicating the high potential of this method.

Moreover, it might indirectly reflect nerve regeneration. In our pilot study, FR clearly depicted structural changes in the postoperative course with FR returning from pathological to normal. Regarding one of our initial questions, our findings underline the possible applicability of this method to indirectly assess regenerative processes in the postoperative period. But, in our setting HRNS could not depict regenerating axons in the nerve. This is supported by the fact that FR was normal in n = 1 patient in the most likely denervated degenerated nerve portion located distal to the grafting site. With reference to our questions raised with this pilot study, the results suggest a positive correlation between clinical and/or electrophysiological recovery. However, further investigations with larger patient samples are required to understand whether FR can reliably predict clinical outcome.

As functional recovery is not only dependent on nerve regeneration, pure "nerve assessment" might not be enough. In future studies, evaluation of muscle status and integration of overall trauma impact on the affected part of the body could be considered as well as central nerve system alterations.

CONCLUSION

To our best knowledge, this is the first study applying FR in HRNS for quantitative assessment of damage and postoperative sonomorphological changes in traumatic peripheral nerve lesions in correlation to clinical course in humans. Our results revealed significant differences for FR values between healthy and lesioned nerves. Furthermore, there is a significant structural change towards a "healthy" aspect following surgery corresponding to clinical recovery. Therefore, this method might potentially advance the assessment of nerve trauma and could be a valuable tool to indirectly monitor structural nerve regeneration. This is a pilot study, and further evaluation with longer follow-up periods in larger patient groups is required.

Disclosures

Substantial work has been performed using the fund of "Intramuraler Forschungspool der Falkultät VI" of Carl-von-Ossietzky-University Oldenburg, Germany. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

A very interesting approach toward understanding important outstanding peripheral nerve issues using high-resolution ultrasound: namely how to distinguish normal from abnormally traumatized nerve; and successfully recovering and regenerating nerve from persistently damaged nerve without evidence of functional motor recovery. This study is an interesting first step that raise more questions than it answers, not unusual for pilot studies. However, the authors could and should do more work to answer some questions that they raised and could have answered.

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This work was partially presented in the annual meeting of the Spanish Society of Neurology (LXIX Reunión Anual de la Sociedad Española de Neurología) in Valencia, Spain, November 24, 2017, as an oral communication.

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Received, April 30, 2018.
Accepted, September 30, 2018.
Published Online, November 8, 2018.

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Radiological Characteristics and Natural History of Adult *IDH*-Wildtype Astrocytomas with *TERT* Promoter Mutations

BACKGROUND: Adult *IDH*-wildtype astrocytomas with *TERT* promoter mutations (*TERTp*) are associated with a poor prognosis.

OBJECTIVE: To analyze the radiological presentation and natural history of adult *IDH*-wildtype astrocytomas with *TERTp*.

METHODS: We retrospectively reviewed the characteristics of 40 *IDH*-wildtype *TERTp*-mutant astrocytomas (grade II n = 19, grade III n = 21) and compared them to those of 114 *IDH*-mutant lower grade gliomas (LGG), of 92 *IDH*-wildtype *TERTp*-mutant glioblastomas, and of 15 *IDH*-wildtype *TERTp*-wildtype astrocytomas.

RESULTS: Most cases of *IDH*-wildtype *TERTp*-mutant astrocytomas occurred in patients aged >50 yr (88%) and presented as infiltrative lesions without contrast enhancement (73%) that were localized in the temporal and/or insular lobes (37.5%) or corresponded to a gliomatosis cerebri (43%). Thalamic involvement (33%) and extension to the brainstem (27%) were frequently observed, as was gyriform infiltration (33%). This radiological presentation was different from that of *IDH*-mutant LGG, *IDH*-wildtype *TERTp*-mutant glioblastomas, and *IDH*-wildtype *TERTp*-wildtype astrocytomas. Tumor evolution before treatment initiation was assessable in 17 cases. Ten cases demonstrated a rapid growth characterized by the apparition of a ring-like contrast enhancement and/or a median velocity of diametric expansion (VDE) ≥8 mm/yr but 7 cases displayed a slow growth (VDE <8 mm/yr) that could last several years before anaplastic transformation. Median overall survival of *IDH*-wildtype *TERTp*-mutant astrocytomas was 27 mo.

CONCLUSION: *IDH*-wildtype *TERTp*-mutant astrocytomas typically present as nonenhancing temporo-insular infiltrative lesions or as gliomatosis cerebri in patients aged >50 yr. In the absence of treatment, although rapid tumor growth is frequent, an initial falsely reassuring, slow growth can be observed.

KEY WORDS: *IDH*-wildtype astrocytoma, Lower grade gliomas, Telomerase reverse transcriptase promoter

Neurosurgery 85:E448–E456, 2019 DOI:10.1093/neuros/nyy513 www.neurosurgery-online.com

World Health Organization (WHO) grade II (low grade) and grade III (anaplastic) adult diffuse gliomas form a heterogeneous group of neoplasms, also known as "lower grade gliomas" (LGG). From a molecular point of view, 3 main subgroups of adult LGG can be distinguished.[1,2] LGG with the 1p/19q codeletion have the best prognosis, *IDH*-mutant LGG, without 1p/19q codeletion, have an intermediate prognosis, and the non-1p/19q codeleted and *IDH*-wildtype LGG generally have the poorest prognosis. The latter, however, corresponds to a heterogeneous group of tumors. In the revised 2016 WHO brain tumor classification, it is considered as a provisional entity and is referred to as "diffuse and anaplastic astrocytoma, *IDH*-wildtype."[3] *H3F3A K27M* mutations are by definition absent in *IDH*-wildtype astrocytomas as the presence of these mutations defines *H3K27M*-mutant diffuse midline gliomas which are considered as

ABBREVIATIONS: FLAIR, fluid-attenuated inversion recovery; **GBM,** glioblastoma; **LGG,** lower grade gliomas; **MRI,** magnetic resonance imaging; **MTD,** mean tumor diameter; **OS,** overall survival; ***TERTp,*** TERT promoter; **VDE,** velocity of diametric expansion; **WHO,** World Health Organization

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grade IV.[4] Several studies have shown that *IDH*-wildtype astrocytomas can be split into subgroups with different outcomes according to O6-methylguanine-DNA methyltransferase (*MGMT*) methylation status,[5] chromosome 7 gain and chromosome 10 loss,[6-8] *EGFR* amplification,[9] methylation profiling, gene expression profiling,[10] and *TERT* promoter (*TERTp*) mutation status.[2,9,11-15] *TERTp* mutations are a hallmark of *IDH*-wildtype glioblastomas (GBM) and occur in 80% of these tumors.[15] In patients with *IDH*-wildtype astrocytoma, the presence of a *TERTp* mutation has been consistently found to be associated with a poor prognosis irrespective of chromosome 7 gain and chromosome 10 loss.[2,9,11-16] The characteristics of *IDH*-wildtype *TERTp*-mutant astrocytomas, however, remain to be fully described.[15,17] Herein, in order to better characterize these gliomas, we analyzed their imaging and growth characteristics and compared them to those of a series of *IDH*-mutant LGG, *IDH*-wildtype *TERTp*-mutant GBM, and *IDH*-wildtype *TERTp*-wildtype astrocytomas.

METHODS

We retrospectively identified all adult patients with a diagnosis of *IDH*-wildtype *TERTp*-mutant astrocytoma diagnosed in our center between January 2011 and September 2017 and reviewed their clinical, radiological, histological, and molecular characteristics. The list of patients with a diagnosis of *IDH*-wildtype *TERTp*-mutant astrocytoma was retrospectively obtained from the records of the neuropathology department and matched with the records of the neuro-oncology department. Patients were included if they were aged ≥18 yr, had a grade II or III *IDH*-wildtype astrocytoma according to 2016 WHO brain tumor classification, had a *TERTp* mutation, had no *IDH1*, *IDH2*, *H3F3A*, or *HIST1H3B* mutation, had an available magnetic resonance imaging (MRI) for radiological review, and no ring-like contrast enhancement at diagnosis. The characteristics of *IDH*-wildtype *TERTp*-mutant astrocytomas were compared to those of contemporaneous series of grade II and III *IDH*-mutant LGG, *IDH*-wildtype *TERTp*-mutant GBM, and grade II and III *IDH*-wildtype *TERTp*-wildtype astrocytomas. Patients of these comparative series were retrospectively identified and included if they were aged ≥18 yr, had an available MRI for radiological review, had a grade II or III *IDH*-mutant glioma or an *IDH*-wildtype *TERTp*-mutant GBM or a grade II and III *IDH*-wildtype *TERTp*-wildtype astrocytomas according to 2016 WHO brain tumor classification.

IDH1/2, H3F3A/HIST1H3B, BRAF V600E, and *TERTp* mutations, *EGFR* gene amplification, *MGMT* promoter methylation, and loss of heterozygosity of chromosomes 1p and 19q by codeletion were assessed as previously described.[4,18,19] *IDH1/2* mutations status was available in all cases and *MGMT* promoter methylation and *EGFR* amplification status in most cases. *H3F3A/HIST1H3B* and BRAF V600E mutation status were available in all cases of *IDH*-wildtype astrocytoma. *TERTp* mutations were available in all cases of *IDH*-wildtype *TERTp*-mutant astrocytoma, *IDH*-wildtype *TERTp*-mutant GBM, and *IDH*-wildtype *TERTp*-wildtype astrocytoma. The 1p/19q codeletion status was available in most cases of *IDH*-mutant LGG.

Brain MRI scans were independently reviewed by 2 investigators (C.I. and F.D.) for the location of T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity, the presence and type (patchy, nodular, homogeneous, ring-like) of parenchymal contrast enhancement, the presence of a gliomatosis (defined as the involvement of 3 or more lobes), the presence of a gyriform infiltration (defined as an area of FLAIR hyperintensity limited to the cortical grey matter), as well as abnormalities on proton magnetic resonance spectroscopy (1H-MRS) and dynamic contrast-enhanced perfusion MRI. In patients with *IDH*-wildtype *TERTp*-mutant astrocytoma in whom at least 2 consecutive MRIs (in DICOM format) before treatment initiation were available with a minimal delay of 1.5 mo between the 2 exams, we estimated the slope of the growth curve of the mean tumor diameter (MTD; ie, the velocity of diametric expansion—VDE). For this purpose, the tumor margins were outlined on FLAIR images using the OsiriX Lite version 9.0.1 (Pixmeo SARL, Geneva, Switzerland), and tumor volume was automatically calculated on the basis of multiple manually defined regions of interest. The final volume was obtained in mm^3 and the MTD was calculated using the formula: $MTD = (2 \times V)^{1/3}$. Linear regressions of the MTD of each patient vs time were subsequently performed.[19,20] Patients were stratified according to VDE; rapid growth (VDE ≥8 mm/yr) and slow growth (VDE <8 mm/yr).[21]

Categorical comparisons were performed using Fisher's exact test, and a t-test was used for quantitative variables. The survival time was measured from the date of the histological diagnosis to the date of last follow-up or death. Survival was estimated using the Kaplan-Meier method, and differences between curves were assessed using the Log-rank test. The median follow-up time since histological diagnosis was estimated using the reverse Kaplan-Meier method. All calculations were performed using SPSS software package version 18.0 (SPSS Inc, IBM Corp, Armonk, New York), and *P* values <.05 were considered significant.

Study design and manuscript organization were guided by the STROBE statement on cohort studies. The study was approved by the Institutional Review Board. Given the retrospective nature of this study, in accordance with our institutional policy, informed consent was not required for the individuals included for analysis.

RESULTS

Patient and Tumor Characteristics

Forty-six patients with a diagnosis of *IDH*-wildtype *TERTp*-mutant astrocytoma were retrospectively identified. After excluding 6 patients in whom a sampling error was suspected because of the presence of a ring-like contrast enhancement on MRI, 40 patients were included. Their characteristics are summarized in Table. Most patients were aged ≥50 yr (n = 35, 88%).

Nineteen patients had a grade II (47%) and twenty-one patients a grade III (53%) *IDH*-wildtype astrocytoma. The median Ki67 labeling was 8% (range: 0%-40%). TP53 staining was positive (>10%) in 4/34 cases (12%), and ATRX expression was retained in all 17 cases in which it was studied. The *TERTp* mutation was a C228T in 29 cases (72.5%) and a C250T in 11 cases (27.5%). All cases were *H3F3A*, *HIST1H3B*, BRAF V600E wildtype. An *EGFR* amplification was present in 9 out of 39 patients (23%), and was more frequent in grade III than in grade II tumors (8/21 grade III vs 1/18 grade II; *P* = .02). The *MGMT* promoter was methylated in 13/35 patients (37%). As expected, all cases in which the 1p/19q codeletion was tested (n = 20) were 1p/19q-retained.

TABLE. Summary and Comparison of the Characteristics of IDH-Wildtype TERT Promoter Mutant Astrocytomas with Other Histomolecular Subtypes

	IDHwt TERTp-mtAstro.	IDHmt LGG	[a]	TERTp-mt GBM	[b]	IDHwt TERTp-wtAstro.	[c]
n	40	114		92		15	
Median age,[d] yr	61 (42-81)	42.7 (23-81)	<.001	66 (36-91)	0.19	40 (18-67)	<.001
Sex ratio F/M	0.9/1	0.65/1		1.1/1		0.9/1	
Clinical presentation at diagnosis, n (%)							
Seizures	21/40 (53)	83/113 (73)	0.02	33/87 (38)	0.17	2/15 (13)	0.01
Focal deficit	10/40 (25)	6/113 (5)	0.001	29/87 (3)	0.41	11/15 (73)	0.002
Cognitive deficit	5/40 (12)	6/113 (5)	0.16	10/87(1)	0.88	1/15 (7)	0.9
Headache	2/40 (5)	11/113 (10)	0.52	11/87 (13)	0.23	2/15 (13)	0.3
Casual	2/40 (5)	7/113 (6)	0.78	4/87 (5)	0.92	0/15	0.99
Radiological characteristics, n (%)							
Location							
Frontal	24/40 (60)	93/114 (82)	0.01	33/92 (36)	0.01	4/15 (2)	0.04
Parietal	14/40 (35)	21/114 (18)	0.05	26/92 (28)	0.54	0/15	0.006
Temporal	28/40 (70)	49/114 (43)	0.005	44/92 (48)	0.02	2/15 (13)	<.001
Insula	26/40 (65)	43/114 (38)	0.005	28/92 (30)	<.001	2/15 (13)	<.001
Occipital	2/40 (5)	2/114 (2)	0.27	13/92 (14)	0.23	0/15	0.99
Thalamus	13/40 (33)	6/114 (5)	<.001	9/92 (10)	0.002	4/15 (26)	0.75
Brainstem	11/40 (27)	5/114 (4)	<.001	8/92 (9)	0.007	8[e]/15 (53)	0.11
Gliomatosis							
Yes	17/40 (43)	10/114 (9)	<.001	12/92(13)	<.001	1/15 (7)	0.01
No	23/40 (57)	104/114 (91)		80/92 (87)		13/15 (93)	
Gyriform infiltration							
Yes	13/40 (33)	3/114 (3)	<.001	14/92 (15)	0.002	0/15	0.01
No	27/40 (67)	111/114 (9)		78/92 (85)		15/15 (100)	
Contrast enhancement							
Yes	11/40 (27)	40/111 (35)	–[g]	84/91 (91)	–[g]	9/15 (60)	–[g]
No	29/40 (73)	71/111 (65)		7/91 (9)		6/15 (40)	
WHO grade, n (%)							
Grade II	19/40 (47)	76/114 (67)	0.04			7/15 (46)	0.99
Grade III	21/40 (53)	38/114 (33)				8/15 (54)	
Grade IV				92/92 (100)			
Molecular characteristics,[f] n (%)							
IDH mt.	0/40	114/114 (100)	–	0/92	–	0/15	–
1p/19q codel.	0/20	50/106 (47)	–	NA	–	0/3	–
MGMT meth.	13/35 (37)	65/85 (76)	<.001	43/85(5)	0.22	10/10 (100)	0.006
EGFR amp.	9/39 (23)	2/76 (3)	0.001	32/87 (37)	0.15	1/15	0.25
H3 K27M mt.	0/39	NA	–	0/52	–	0/15	–

IDH: isocitrate dehydrogenase; IDHwt: *IDH*-wildtype; TERTp-mt: *TERT* promoter mutation; Astro: Astrocytoma; IDHmt: *IDH* mutant; LGG: lower grade gliomas; GBM: glioblastoma; TERTp-wt: *TERT* promoter wildtype; yr: years old; F/M: female/male; WHO: World Health Organization; 1p/19q codel: 1p/19q codeletion; NA: not available; MGMT meth: *MGMT* promoter methylation, EGFR amp: *EGFR* amplification; H3K27M mt: *H3K27M* mutation.

Comparison between.

[a] *IDH*wt *TERTp*-mt astrocytomas and *IDH*mt LGG.

[b] *IDH*wt *TERT*p-mt astrocytomas and *IDH*wt *TERT*p-mt GBM.

[c] *IDH*wt *TERTp*-mt astrocytomas and *IDH*wt *TERTp*-wt astrocytomas.

[d] Median (range).

[e] This includes 2 cases that were located in the cerebellum.

[f] ATRX expression was retained in 17/17 *IDH*wt *TERT*p-mt astrocytomas and lost in 4/9 *IDH*wt *TERT*p-wt astrocytomas.

[g] As contrast enhancement was utilized as a criteria to define the *IDH*wt *TERT*p mutant cohort, the rate of contrast enhancement could not be compared across glioma subtypes.

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Radiological Presentation

Radiological characteristics are summarized in Table and representative examples of radiological presentation are shown in Figure 1. Most *IDH*-wildtype *TERTp*-mutant astrocytomas presented as poorly delimited (n = 24, 60%) infiltrative lesions without contrast enhancement (n = 28, 73%) that were localized in the temporal and/or insular lobes (n = 15, 37%) or corresponded to a gliomatosis cerebri (n = 17, 43%). When present, contrast enhancement was patchy (n = 7, 18%) or nodular (n = 4, 10%). In 13 patients (33%), the thalamus was affected, and in 11 patients (27%) the supratentorial infiltration extended to the brainstem but in none of the patients the tumor was restricted to the brainstem. In 13 cases (33%), areas of gyriform infiltration were observed which in 4 patients occurred in association with an ipsilateral thalamic involvement without apparent continuity on FLAIR sequences between the cortical and thalamic lesions. Nine patients (23%) presented with multicentric lesions at diagnosis. MRI spectroscopy was performed in 9 grade II and 5 grade III *IDH*-wildtype *TERTp*-mutant astrocytomas; it found a metabolic profile suggestive of an aggressive glioma in 11 cases (79%; grade II n = 8, grade III n = 3) because of the presence of an elevated Cho/Naa ratio (>2, n = 11) and/or of lipid/lactate peaks (n = 5). In contrast, dynamic contrast-enhanced perfusion MRI which was performed in 15 patients found an elevated (>1.7) intratumoral relative cerebral blood flow in 3 patients (20%). The radiological presentation of *IDH*-wildtype *TERTp*-mutant astrocytomas was neither associated with histological grade (grade II vs grade III), *EGFR* amplification nor with *MGMT* methylation.

Natural History

Twenty-one patients (12 patients followed before histological diagnosis, 4 patients before and after histological diagnosis, and 5 patients after histological diagnosis) underwent at least 2 MRI exams before treatment initiation; the median interval between the 2 exams was 5.5 mo (range: 0.3-48.3 mo). Apparition of a ring-like contrast enhancement was observed in 6 patients (29%) after a median interval of 2.8 mo (range: 0.26-4.5); no new contrast enhancement was observed in the other 15 patients after a median interval of 8.3 mo (range: 1.2-48.3 mo). In the 17 patients in whom the duration of radiological follow-up before treatment initiation enabled volumetric analysis (median: 6.5 mo, range: 1.5-48 mo), the median VDE was 9.4 mm/yr (range: 0.7-66 mm/yr). Ten patients (59%, grade II n = 5, grade III n = 5) presented a rapid tumor growth (≥8 mm/yr, median VDE: 19.6 mm/yr) which was associated with a new ring-like contrast enhancement in 4 patients. Seven patients (41%, grade II: n = 5, grade III: n = 2) presented a slow growth (<8 mm/yr, median VDE: 4.6 mm/yr) which in 4 patients lasted for 1 to 4 yr before evidence of anaplastic transformation on MRI. Slow vs rapid growth was not associated with grade, *EGFR* amplification or *MGMT* methylation. The median growth rate of grade II and grade III *IDH*-wildtype *TERTp*-mutant astrocytomas was similar (9.3 vs 9.4 mm/yr, $P = .9$). Representative examples of the natural history of *IDH*-wildtype *TERTp*-mutant astrocytomas are presented in Figure 2.

Treatment and Outcome

Surgery consisted of a biopsy in most patients (n = 34, 85%). Five patients underwent a partial (12.5%) and 1 a complete resection (2.5%). After histological diagnosis, treatment of grade II *IDH*-wildtype *TERTp*-mutant astrocytomas (n = 19) consisted of temozolomide radiochemotherapy (n = 6, 31.6%), temozolomide (n = 5, 26.3%), PCV (procarbazine, CCNU, and vincristine) chemotherapy (n = 2, 10.5%), radiotherapy alone (n = 1, 5.3%), and of a wait and scan strategy (n = 5, 26.3%). Among the latter, 1 patient died a year after diagnosis due to status epilepticus, 2 initiated an oncological treatment because of a clinical or radiological progression within 6 mo after diagnosis, and 2 were still being followed 1.5 and 4 yr after the histological diagnosis. Treatment of patients with grade III *IDH*-wildtype *TERTp*-mutant astrocytoma (n = 21) consisted of temozolomide radiochemotherapy (n = 13, 62%), of radiotherapy with PCV (n = 1, 4.7%), of radiotherapy alone (n = 1, 4.7%), of an initial wait and scan strategy (n = 1, 4.7%) and of temozolomide alone in 5 patients (24%) who had an extended gliomatosis or were considered too fragile to receive temozolomide radiochemotherapy.

At last news, after a median follow-up of 20 mo, 16 patients had died. Median overall survival (OS) since histological diagnosis was 27 mo in the entire series (Figure 3), 27 mo in patients with grade II and 24 mo in patients with grade III *IDH*-wildtype *TERTp*-mutant astrocytoma ($P = .4$). The median OS since initial neuroimaging in the entire series was 33.6 mo. OS was not associated with radiological presentation or with slow vs rapid growth.

Comparison of the Characteristics of *IDH*-wildtype *TERTp*-mutant Astrocytomas with Other Glioma Subtypes

The comparison of the characteristics of *IDH*-wildtype *TERTp*-mutant astrocytomas with those of a series of 114 *IDH*-mutant LGG, 92 *IDH*-wildtype *TERTp*-mutant GBM, and 15 *IDH*-wildtype *TERTp*-wildtype astrocytomas is summarized in Table. Patients with *IDH*-wildtype *TERTp*-mutant astrocytoma were older and more frequently aged ≥50 yr (87.5% vs 25.4%, $P < .001$) at diagnosis than those with *IDH*-mutant LGG and had a different radiological presentation irrespective of grade and 1p/19q codeletion status (data not shown). Despite similar age at diagnosis and a similar rate of *EGFR* amplification and *MGMT* promoter methylation, the radiological presentation of *IDH*-wildtype *TERTp*-mutant astrocytomas was different from that of *IDH*-wildtype *TERTp*-mutant GBM. Compared to *IDH*-mutant LGG and to *IDH*-wildtype *TERTp*-mutant GBM, *IDH*-wildtype *TERTp*-mutant astrocytomas was significantly more frequently involved the temporal lobe (respectively, $P = .005$

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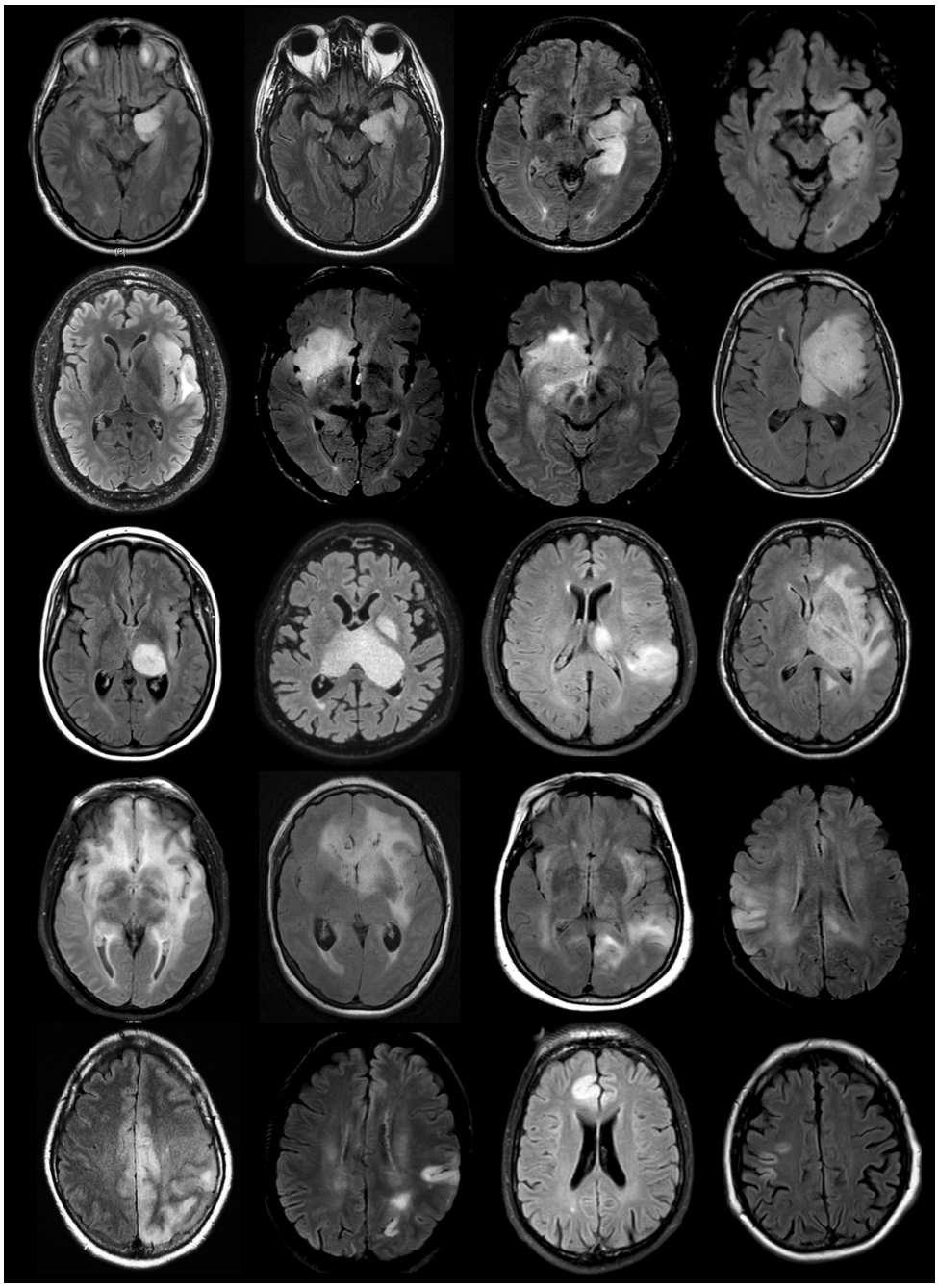


FIGURE 1. *MRI findings at diagnosis in patients with IDH-wildtype TERTp-mutant astrocytomas. Representative axial FLAIR sequences of IDH-wildtype TERTp-mutant astrocytomas with a temporal and insular location (first and second row), with unilateral or bilateral thalamus involvement (third row), with a gliomatosis aspect (fourth row), and with a gyriform infiltration (last row).*

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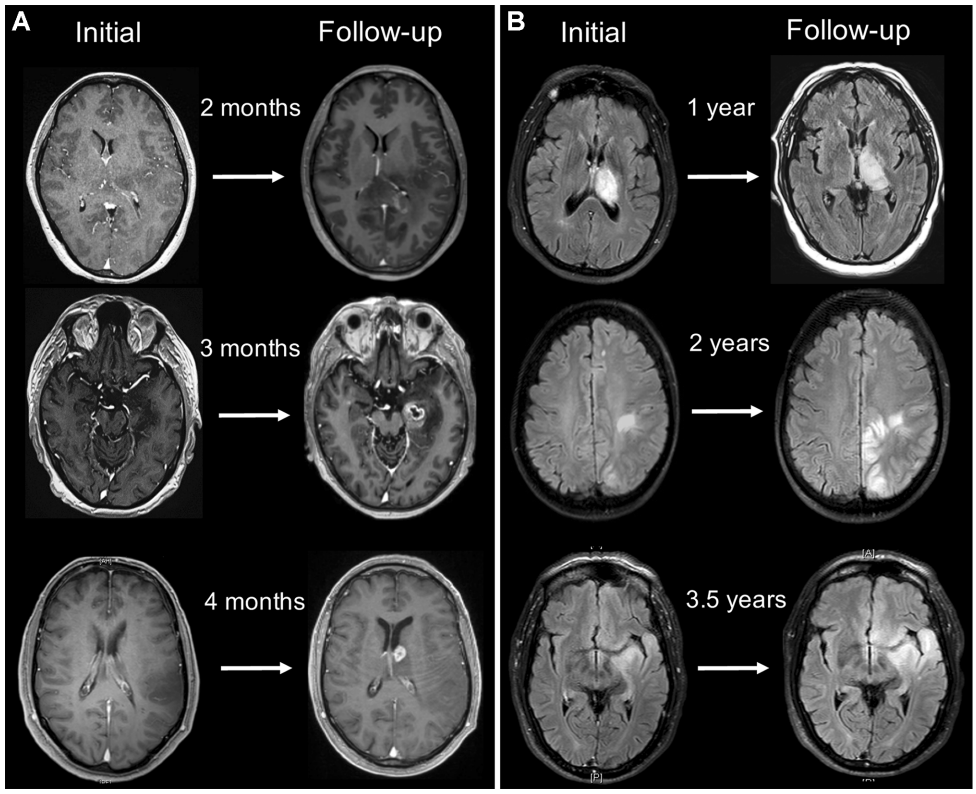


FIGURE 2. *Examples of the natural history of IDH-wildtype TERTp-mutant astrocytomas.* **A**, *Axial T1 with gadolinium infusion MRI sequences in 3 cases characterized by a rapid apparition of a ring-like contrast enhancement before treatment initiation (left: at histological diagnosis; right: at follow-up). From top to bottom: IDH-wildtype TERTp-mutant grade II astrocytoma in a 42-yr-old patient (survival: 27 mo), IDH-wildtype TERTp-mutant grade II astrocytoma in a 66-yr-old patient (survival: 12 mo), and IDH-wildtype TERTp-mutant grade II astrocytoma in a 72-yr-old patient (survival: 16 mo).* **B**, *Axial FLAIR sequences (left: at first imaging; right: at the time of histological diagnosis) in 3 cases characterized by an initial slow growth and managed with an initial wait and scan strategy. From top to bottom: A IDH-wildtype TERTp-mutant EGFR-amplified grade III astrocytoma in a 78-yr-old patient (survival: 22 mo), IDH-wildtype TERTp-mutant grade II astrocytoma in a 55-yr-old patient (survival 27 mo), and IDH-wildtype TERTp-mutant grade II astrocytoma in a 66-yr-old patient (alive 48 mo after first MRI).*

and $P = .02$), the insula (respectively, $P = .005$ and $P < .001$), the thalamus (respectively, $P < .001$ and $P = .002$), and the brainstem (respectively, $P < .001$ and $P = .007$). They also more frequently presented as gliomatosis (respectively, $P < .001$ and $P < .001$) and displayed a higher rate of gyriform infiltration (respectively, $P < .001$ and $P = .02$). The clinical and the radiological presentation of *IDH*-wildtype *TERTp*-mutant astrocytomas also differed from that of *IDH*-wildtype *TERTp*-wildtype astrocytomas. The differences observed between *IDH*-wildtype *TERTp*-mutant astrocytomas and the other glioma subtypes remained significant when the 6 cases of *IDH*-wildtype *TERTp*-mutant astrocytomas excluded because of a ring-like contrast enhancement were included in the analysis.

As shown on Figure 3, the median OS of patients with *IDH*-wildtype *TERTp*-mutant astrocytoma was longer than that of those with GBM (27 vs 13 mo, $P = .005$) and shorter than that of patients with *IDH*-wildtype *TERTp*-wildtype astrocytoma (27 vs 58 mo, $P = .17$) and that of those with *IDH*-mutant LGG (27 mo vs not reached, $P < .001$).

DISCUSSION

Early identification of poor prognosis gliomas is important to enable rapid diagnosis and treatment. Herein, we show that *IDH*-wildtype *TERTp*-mutant astrocytomas typically present as nonenhancing temporoinsular infiltrative lesions or as gliomatosis cerebri in patients aged ≥50 yr. In the absence of treatment, rapid growth and apparition of GBM-like characteristics are frequently observed, yet some of these tumors display an initial, falsely reassuring low-grade glioma-like slow growth.

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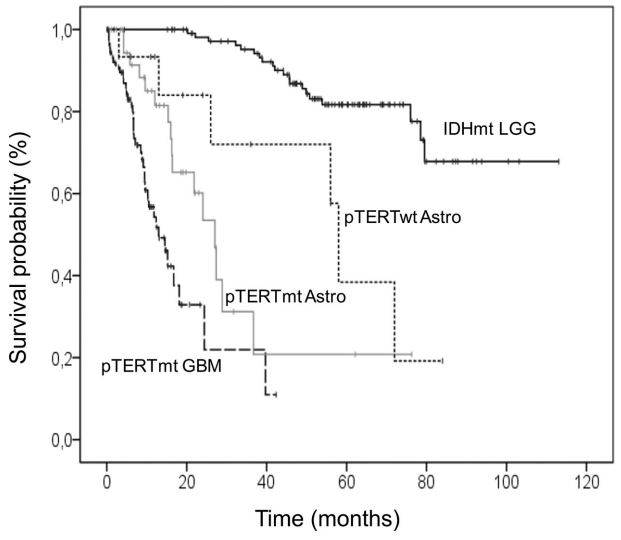


FIGURE 3. *Kaplan-Meier estimates of OS in IDH-wildtype TERTp-mutant astrocytomas and in other histomolecular subtypes. IDHmt LGG: IDH-mutant lower grade gliomas (n = 114), pTERTwt Astro: IDH-wildtype TERTp-wildtype astrocytoma (n = 15); pTERTmt Astro: IDH-wildtype TERTp-mutant astrocytomas (n = 40), TERTp-mutant GBM: IDH-wildtype TERTp-mutant GBM (n = 92).*

IDH-wildtype *TERTp*-mutant grade II and III astrocytomas account for approximately 10% of LGG and for 20% to 30% of *IDH*-wildtype *TERTp*-mutant gliomas (the majority of these gliomas corresponding to *IDH*-wildtype GBM).[2,15] Previous studies have shown that *IDH*-wildtype LGG have a frequent temporoinsular location and a more diffusely infiltrative pattern compared to *IDH*-mutant LGG.[22-25] To the best of our knowledge, however, the present study is the first to specifically analyze the radiological characteristics and the natural history of *IDH*-wildtype *TERTp*-mutant astrocytomas. Since most *IDH*-wildtype *TERTp*-mutant astrocytomas present as noncontrast-enhancing lesions, they may wrongly suggest an *IDH*-mutant low-grade glioma, especially when they have a slow growth which in the present study was the case in nearly half of the patients in whom pretreatment evolution was assessable. Features that may help to suspect *IDH*-wildtype *TERTp*-mutant astrocytomas in the preoperative setting are age at diagnosis ($\geq$50 yr in most cases), temporoinsular location, and the presence of a gliomatosis, gyrifom infiltration, and thalamic involvement, as well as a brainstem extension. As observed herein, MR spectroscopy may also be helpful to suspect an aggressive glioma despite the absence of contrast enhancement while perfusion MRI may be falsely reassuring. The radiological presentation of *IDH*-wildtype *TERTp*-mutant astrocytomas also differed from that of *IDH*-wildtype *TERTp*-wildtype astrocytomas in which MRI characteristics were rarely suggestive of an *IDH*-mutant LGG (3 patients only), due to frequent posterior fossa location and homogeneous contrast enhancement. A striking characteristic of *IDH*-wildtype *TERTp*-mutant astrocytoma radiological presentation was the high rate of gliomatosis cerebri. In the 2016 WHO brain tumor classification, gliomatosis cerebri is no longer considered as a distinct entity as it has been shown to comprise a genetically heterogeneous group of gliomas.[3,26,27] *IDH*-wildtype *TERTp*-mutant astrocytomas also frequently presented a distinct pattern of cortical grey matter infiltration. To the best of our knowledge, gyriform infiltration, ie, elective cortical grey matter infiltration, has not been reported as a distinctive radiological feature. Herein, we observed that this characteristic was significantly more frequent in *IDH*-wildtype *TERTp*-mutant astrocytomas than in other molecular subtypes of gliomas. However, it is interesting to note that gyriform infiltration was also significantly more frequent in *IDH*-wildtype *TERTp*-mutant GBM than in *IDH*-mutant LGG and in *IDH*-wildtype *TERTp*-wildtype astrocytomas, further supporting the association between this feature and the presence of an *IDH*-wildtype *TERTp*-mutant molecular profile. Another distinctive characteristic of *IDH*-wildtype *TERTp*-mutant astrocytomas was the high rate of thalamus location and of brainstem extension. *H3K27M* mutations, which rarely associate with *TERTp* mutations, have been reported in half of adult thalamic gliomas.[4,28] The present study suggests that *TERTp* mutations occur in a subset of *H3K27M*-wildtype thalamic gliomas.

Given similarities regarding age at diagnosis, molecular profile, and outcome, it has been hypothesized that *IDH*-wildtype *TERTp*-mutant astrocytomas may correspond to under-sampled GBM or to GBM diagnosed at an early stage of evolution just before the apparition of microvascular proliferation and necrosis.[1,2,9,15] The question has therefore been raised of whether these gliomas should be considered as unrecognized GBM.[1,2,9,15] The present study indicates that although *IDH*-wildtype *TERTp*-mutant astrocytomas frequently develop GBM-like characteristics within a few months after diagnosis, there are significant differences regarding the radiological presentation of *IDH*-wildtype *TERTp*-mutant astrocytomas and GBM. In addition, a subset of *IDH*-wildtype *TERTp*-mutant astrocytomas is characterized by an initial slow growth and, as previously reported, although poor, the prognosis of these gliomas is still better than that of GBM.[2,14] In our opinion, these findings support distinguishing *IDH*-wildtype *TERTp*-mutant astrocytomas from GBM. It has recently been proposed that LGG with GBM-like molecular characteristics may be considered as "grade III GBM."[17] The present study suggests that *IDH*-wildtype *TERTp*-mutant astrocytomas could be classified in this category. Grading (grade II vs grade III) has been shown to be associated with a strong prognostic value in *IDH*-wildtype astrocytomas,[29,30] it is unknown however whether this finding remains true in *IDH*-wildtype astrocytomas with *TERTp* mutation. In the series reported herein, the outcome of grade II and grade III *IDH*-wildtype *TERTp*-mutant astrocytomas was not significantly different.

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As reflected by the treatment heterogeneity in our series, the optimal therapeutic strategy in *IDH*-wildtype *TERTp*-mutant astrocytomas remains to be established. Within recent years, clinicians have become inclined to treat LGG with GBM-like molecular characteristics as GBM.[17] Consistently, the present study shows that even slow-growing *IDH*-wildtype *TERTp*-mutant astrocytomas are associated with a poor prognosis and that, with a few exceptions, a wait and scan strategy is not a reasonable option in these tumors. In the future, however, the classification of *IDH*-wildtype *TERTp*-mutant astrocytomas may be refined based on the integration of additional molecular alterations. Although *IDH*-wildtype *TERTp*-mutant astrocytomas have distinct radiological characteristics, the radiological presentation and the natural history of these gliomas is variable. The molecular characteristics accounting for this heterogeneity, as well as those accounting for the differences between *IDH*-wildtype *TERTp*-mutant astrocytomas and GBM, remain to be identified. Herein, *EGFR* amplification and *MGMT* methylation were not associated with the radiological presentation nor with the growth characteristics of *IDH*-wildtype *TERTp*-mutant astrocytomas and the rate of these alterations was similar in these gliomas and in *IDH*-wildtype GBM. Chromosome 7 gain and chromosome 10 loss occur in most *IDH*-wildtype GBM and in 74% of *IDH*-wildtype *TERTp*-mutant astrocytomas.[16] These alterations are therefore unlikely to explain the differences between *IDH*-wildtype *TERTp*-mutant astrocytomas and GBM but could account for some of the heterogeneity of *IDH*-wildtype *TERTp*-mutant astrocytomas. Indeed, it has recently been shown that the absence of chromosome 7 gain and chromosome 10 loss (26% of cases) was associated with a worse prognosis in *IDH*-wildtype *TERTp*-mutant astrocytomas.[16] FGFR-TACC gene fusions, which occur in a small subset of *IDH*-wildtype *TERTp*-mutant astrocytomas, could also be associated with a distinct radiological presentation.[31]

Limitations

Other than the limited sample size and its retrospective design, the present study is limited by incomplete ATRX mutation status assessment and the absence of comprehensive molecular analysis, especially the absence of chromosome 7 and 10 alterations and of FGFR-TACC fusion analysis. In addition, cases in which analysis of the natural history was possible may correspond to cases in which a less aggressive course permitted a longer interval before treatment onset and may therefore not be fully representative of the *IDH*-wildtype *TERTp*-mutant astrocytoma population. Finally, our results will need to be validated in an independent and larger series and the diagnostic value of the radiological characteristics associated with *IDH*-wildtype *TERTp*-mutant, especially the gyriform infiltration pattern, will have to be assessed in a blinded study. Nevertheless, our study provides for the first time a picture of *IDH*-wildtype *TERTp*-mutant astrocytomas radiological presentation and natural history that will help managing patients with these poor prognosis gliomas.

CONCLUSION

In conclusion, *IDH*-wildtype *TERTp*-mutant astrocytomas are associated with distinct radiological characteristics that may help suspecting these gliomas preoperatively. This is particularly important since these tumors can have an initial falsely reassuring low-grade glioma-like evolution.

Disclosures

Funding was received from Fundación Alfonso Martin Escudero and Association pour la Recherche Contre les Tumeurs Cérébrales to C.I.G. Association pour la Recherche Contre le Cancer (Project n°PJA 20151203400) to Dr Poncet. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgment

The authors thank P. Robinson for English editing.

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Malignant Meningioma: An International Multicentre Retrospective Study

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Received, June 12, 2018.
Accepted, November 20, 2018.
Published Online, December 19, 2018.

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Congress of Neurological Surgeons

BACKGROUND: In contrast to benign meningiomas, malignant meningiomas (MM) are rare and associated with an unfavourable prognosis. Reports on MM concern fairly small cohorts, often comprising less than 30 cases.

OBJECTIVE: To describe the outcome MM and identify factors that may influence survival.

METHODS: Pathology reports and clinical data of 178 patients treated between 1989 and 2017 for a MM at 6 different international institutions were retrospectively reviewed. Seventy-six patients (42.7%) had a previous history of grade I or grade II meningioma. The patients underwent a total of 380 surgical resections and 72.5% received radiotherapy. Median follow-up was 4.5 yr.

RESULTS: At data collection, 111 patients were deceased (63.4%) and only 23 patients (13.7%) were alive without any residual tumor on the most recent scan. Median overall survival was 2.9 yr, 95% confidence interval [CI; 2.4, 4.5]. Overall survival rates at 1, 5, and 10 yr, respectively, were: 77.7%, 95% CI [71.6, 84.3], 40%, 95% CI [32.7, 49], and 27.9%, 95% CI [20.9, 37.3]. In the multivariable analysis, age at MM surgery <65 yr (hazard ratio [HR] = 0.44, 95% CI [0.29, 0.67], $P < .001$), previous benign or atypical meningioma surgery (HR = 1.9, 95% CI [1.23, 2.92], $P = .004$), completeness of resection (HR = 0.51, 95% CI [0.34, 0.78], $P = .002$), and adjuvant radiotherapy (HR = 0.64, 95% CI [0.42, 0.98], $P = .039$) were established as independent prognostic factors for survival.

CONCLUSION: This large series confirms the poor prognosis associated with MM, the treatment of which remains challenging. Patients under 65-yr-old with primary MM may live longer after complete resection and postoperative radiotherapy. Even with aggressive treatments, local control remains difficult to achieve.

KEY WORDS: WHO grade III meningioma, Malignant meningioma, Radiotherapy, Outcome, Prognostic factors

Neurosurgery 85:E461–E469, 2019 DOI:10.1093/neuros/nyy610 www.neurosurgery-online.com

Meningiomas that are thought to arise from arachnoidal cap cells are the most common intracranial extracerebral neoplasm. Three grades of meningioma are recognised by the World Health Organization (WHO) classifications of tumors affecting the central nervous system (CNS).[1] Definition of grade III or malignant meningiomas (MM) includes the following: 20 or more mitoses per 10 high power fields (HPFs); anaplastic cytology resembling that of carcinoma, melanoma, or high-grade sarcoma; or predominant papillary or rhabdoid morphology. While WHO grade I meningiomas occur most often in women and are associated with a relatively good outcome, MM are slightly more frequent in men and have a poor prognosis.[2] They can occasionally spread by metastatic dissemination.[3]

The behavior and outcome of atypical meningiomas (AM) WHO grade II are intermediate.

The relative rarity of MM, with a reported incidence of less than 5 cases for 1 000 000 population per year and a prevalence of less than

ABBREVIATIONS: AM, atypical meningiomas; **CI,** Confidence Interval; **CT,** computed tomography; **GTR,** Gross Total Resection; **HPF,** High Power Field; **HR,** Hazard Ratio; **IQR,** Interquartile Range; **IMRT,** Intensity-Modulated Radiation Therapy; **MRI,** magnetic resonance imaging; **MM,** Malignant Meningiomas; **RT,** Radiotherapy; **STR,** Sub Total Resection; **TERT,** Telomerase Reverse Transcriptase; **TR,** Total Resection; **WHO,** World Health Organization

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3% of all meningiomas, makes it difficult to study their behavior.[4]

For all types of meningioma, maximal safe resection is the treatment of choice, followed by radiotherapy (RT) in cases of MM.[5] What evidence base there is comes from retrospective studies carried out over long periods during which histopathology definitions have changed and during which surgical and radiotherapy (RT) techniques have also evolved. Previous reports on MM have studied fairly small cohorts, often comprising less than 30 cases, rendering it difficult to establish predictors of treatment response and survival. MM are likely to recur regardless of resection status, though less so after complete excision. Most studies have demonstrated some benefit of adjuvant RT, particularly at higher doses.[6]

Objective

The purpose of this study was to investigate the outcome of patients with MM and search for clinical and pathological prognostic factors associated with overall survival.

METHODS

Clinical Material

We performed an international, multicenter, analytical, and retrospective cohort study. Cases were identified from the archives of neurosurgery and neuropathology departments at 6 different centers as follows: the National Hospital for Neurology and Neurosurgery, London (n = 29); the Royal Free Hospital, London (n = 11); The Queen Elizabeth University Hospital, Glasgow (n = 25); Sud Réunion Hospital, Saint-Pierre (n = 9); Pellegrin Hospital, Bordeaux (n = 66); and Sainte-Anne Hospital, Paris (n = 38). Patients diagnosed with a WHO Grade III/malignant/anaplastic/papillary, or rhabdoid meningioma were considered, including patients with relapsing tumor and grade progression. If required, cases diagnosed before 2016 and corresponding to the WHO 2000 or 2007 grading system were reclassified according the latest version. No patient was excluded.

All pathology reports were reviewed but histology slides were not. Data on meningioma sub-type, mitosis count per 10 HPFs (mitotic index), Ki-67 index (MIB-1), presence of necrosis, and brain invasion were separately extracted. In cases of recurrence, histology reports were compared to those from previous resections.

Patient demographic and medical data were collected retrospectively. We used radiographic and surgical reports, and all available in- and outpatient records. Preoperative magnetic resonance imaging (MRI) and/or computed tomography (CT) scans were reviewed when available. Tumor origin was divided into 10 locations but infrequent ones were merged into a new category "other locations."

Surgical resection was assessed by the Simpson grading scale, according to the surgeon's description.[7] Total resection (TR) was defined as Simpson grades I and II, and incomplete or sub total resection (STR) as Simpson grades III, IV, and V. If possible, the surgical impression was compared to the postoperative contrast-enhanced images. In case of radiotherapy, overall dose and time of completion were noted. Mortality was the main outcome of interest. Radiological relapse was defined as evidence of tumor regrowth in case of TR, or progression of any residuum in cases of incomplete resections, on the last contrast-enhanced MRI or CT scan available. Patient outcome and clinical status were assessed through medical records, the patient database of each center, and information obtained from the primary care physicians. A patient with no follow-up data for 2 yr or more was considered to be lost to follow-up and right censored at the time of last follow-up in the survival analysis.

Statistical Methods

Continuous variables are reported as means and standard deviations or as medians and interquartile ranges (IQR); categorical variables are reported as frequencies and proportions. Quantitative variables were categorized according to the median to evaluate their association to the primary outcome. Survival analyses were conducted to delineate factors associated with survival of MM. Outcome was defined as death (event). Survival statistics were based on time to death, which was measured from the date at MM surgery to the date of last follow-up or death.[8] We used the Kaplan–Meier method to estimate the event-free survival and the Mantel Cox log-rank test to compare survival curves. Cox proportional hazards regressions were implemented to identify predictors of death and to estimate Hazard Ratio (HR) with 95% Confidence Intervals (95% CI).[9] Primary analyses were conducted using available cases (available-case analysis). No interactions were considered in the final model. To evaluate the impact of missing data, a sensitivity analysis was run after multiple imputations. A total of 30 imputed datasets were created using multiple imputations by chained equation algorithms with 20 iterations.[10] All variables considered in the multivariable Cox regression model were plugged in the imputation model as well as the event indicator and the cumulative hazard.[11] Final estimations were obtained using Rubin's rules.[10] All tests were 2-sided and statistical significance was defined with an alpha level of 0.05 ($P < .05$). We considered equally any form of radiation therapy in the regression model.

Compliance with Ethical Standards

This study was conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the Helsinki Declaration (2008); to the French data protection authority (CNIL) – an independent national ethical committee, authorization number: 2 008 538; to the STROBE statement for observational studies in epidemiology; and according to the SAMPL guidelines.[12-14] Informed consent was not required due to the retrospective nature of the study.

RESULTS

Population Description and Surgery

Of the 178 cases identified, 88 patients were female (50.6%). Patients' symptoms were mostly related to tumor location, seizures being the most common (Table 1). Seventy-four meningioma (45.7%) were located on the cranial convexity. A total of 380 tumor resections were performed. Fifty-three patients (30.1%) had 2 procedures and 54 (30.7%) had 3 or more. Fifty-six patients (31.8%) had been reoperated on, at least once, for a MM recurrence. Median age at MM surgery was 62.7 yr, IQR [52.1, 71.7]. Ninety-one patients (55.8%) had a TR. A total of 76 patients (42.9%) had had previous surgical procedure for a nonMM, 50 of which were atypical and 26 were benign.

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TABLE 1. Characteristics of the 178 Patients

Characteristics	n, % or median and IQR[a]
Gender (male)	90 (50.6%)
Median age at MM surgery	62.7 yr, IQR [52.1-71.7]
Age at diagnosis <65 yr	101 (53.4%)
Main symptom at presentation	
Motor and walking impairment	22 (15.5%)
Seizure	45 (31.7%)
Cognitive disorders	16 (11.3%)
Dysphasia	5 (3.5%)
Others	51 (28.7%)
Location	
Convexity	74 (45.7%)
Para sagittal/falx	56 (34.6%)
Skull base	17 (10.5%)
Other locations	10 (6.2%)
Side of the meningioma implantation (right vs left)	69 (43.1%
Previous grade I or grade II meningioma surgery	76 (42.9%)
De novo MM	101 (57.1%)
Median number of surgeries for meningioma removal	2, IQR [1-3]
Resection status	
Total resection (TR) (Simpson 1 and 2)	91 (55.8%)
GTR (1, 2, and 3)	108 (66.3%)
Subtotal (STR) (Simpson 3, 4, and 5)	72 (40.4%)
Median mitoses count	21 per 10 HPFs, IQR [12-23]
Median Ki-67 index (MIB-1)	26%, IQR [20-40]
Presence of a brain invasion	79 (59.8%)
Venous sinus invasion	70 (49.3%)
Radiotherapy before MM surgery	34 (22.7%)
Radiotherapy after MM surgery	86 (57.3%)
Chemotherapy	23 (14.8%)
Reoperation for a MM recurrence	56 (31.8%)

[a]IQR: Inter Quartile Range.

Median progression time to malignancy from a previous grade I tumor was 7.5 yr; IQR [4.2-13.6] and 3.2 yr; IQR [1.2-4.9] from a previous grade II tumor, the latter being significantly shorter (*P*-value <.001). Median follow-up was 4.5 yr, IQR [2.1-9.3]. Seventeen patients (9.7%), mostly from overseas, were lost to follow-up (Figure 1).

Radiotherapy

Thirty-four patients received RT before their MM surgery. Only 24 patients with progression from a lower grade (31.6%) received RT compared to 62 patients with de novo MM (61.4%; $P < .001$). Thirteen patients (8.1%) received 2 courses of radiotherapy. The median given dose was 59.4 Gy, IQR [50.4, 60]. Seventy-eight patients (47%) had RT upon MM relapse but were not reoperated on. The median time between the MM surgery and the end of the radiotherapy was 0.3 yr, IQR [0.2-0.4]. Thirty patients (18.4%) did not receive radiotherapy because of poor postoperative functional status, death prior to commencement of radiotherapy, or following clinical decision after complete tumor removal.

Chemotherapy

Twenty-three patients (14.8%) received chemotherapy for tumor progression. Various chemotherapeutic drugs were administered alone or in combination and sometimes sequentially including dacarbazine, hydroxycarbamide, carboplatin, somatostatin, doxorubicin, temozolomide, etoposide, or PCV chemotherapy (procarbazine, lomustine, and vincristine). Chemotherapy did not improve overall survival (HR = 1.2, 95% CI [0.73, 1.98], $P = .48$; Table 2).

Outcome and Survival Analysis

At data collection, 111 patients were dead (63.4%). The median age at death was 68 yr, IQR [57, 74.8]. Six patients died within a month of surgery and 37 within a year. Five patients had disseminated metastatic disease. Median overall survival was 2.9 yr, 95% CI [2.4, 4.5].

Overall survival rates at 1, 5, and 10 yr, respectively, were: 77.7%, 95% CI [71.6, 84.3], 40%, 95% CI [32.7, 49], and 27.9%, 95% CI [20.9, 37.3] (Figure 2).

Significant prognostic factors in univariate analyses were as follows: age at diagnosis, previous benign or atypical meningioma surgery, Simpson grading, and adjuvant radiotherapy. In the multivariable Cox regression analysis, age at MM surgery <65 yr (HR = 0.44, 95% CI [0.29, 0.67], $P < .001$), previous benign or atypical meningioma surgery (HR = 1.9, 95% CI [1.23, 2.92], $P = .004$), completeness of resection (HR = 0.51, 95% CI [0.34, 0.78], $P = .002$), and adjuvant radiotherapy (HR = 0.64, 95% CI [0.42, 0.98], $P = .039$) were established as independent prognostic factors of overall survival (Tables 2 and 3, Figure 3).

Results after multiple imputations were similar (see **Table, Supplemental Digital Content**). At data analysis, only 23 patients (13.7%) were still alive with no visible tumor on their most recent follow-up scan.

DISCUSSION

In this retrospective study of survival after treatment for malignant meningioma, we found that predictors of overall survival were a previous history of benign or atypical meningioma, age at MM surgery, extent of resection, and adjuvant radiotherapy. Our 5-yr overall survival of 40%, 95% CI [32.7, 49] is within the ranges of previously published rates of 28% to 61%, and close to the result found by Orton et al[15] of 41.1% 15,16. Our median survival of 2.9 yr, 95% CI [2.4, 4.5] is also within the ranges of reported results extending from 1.6 to 10.8 years.[15-21]

However, there are notable differences among these reports which suggest possible variations in diagnostic classification and patient management. The lack of consistency in the reported survival rates may be due to the low incidence of MM and/or

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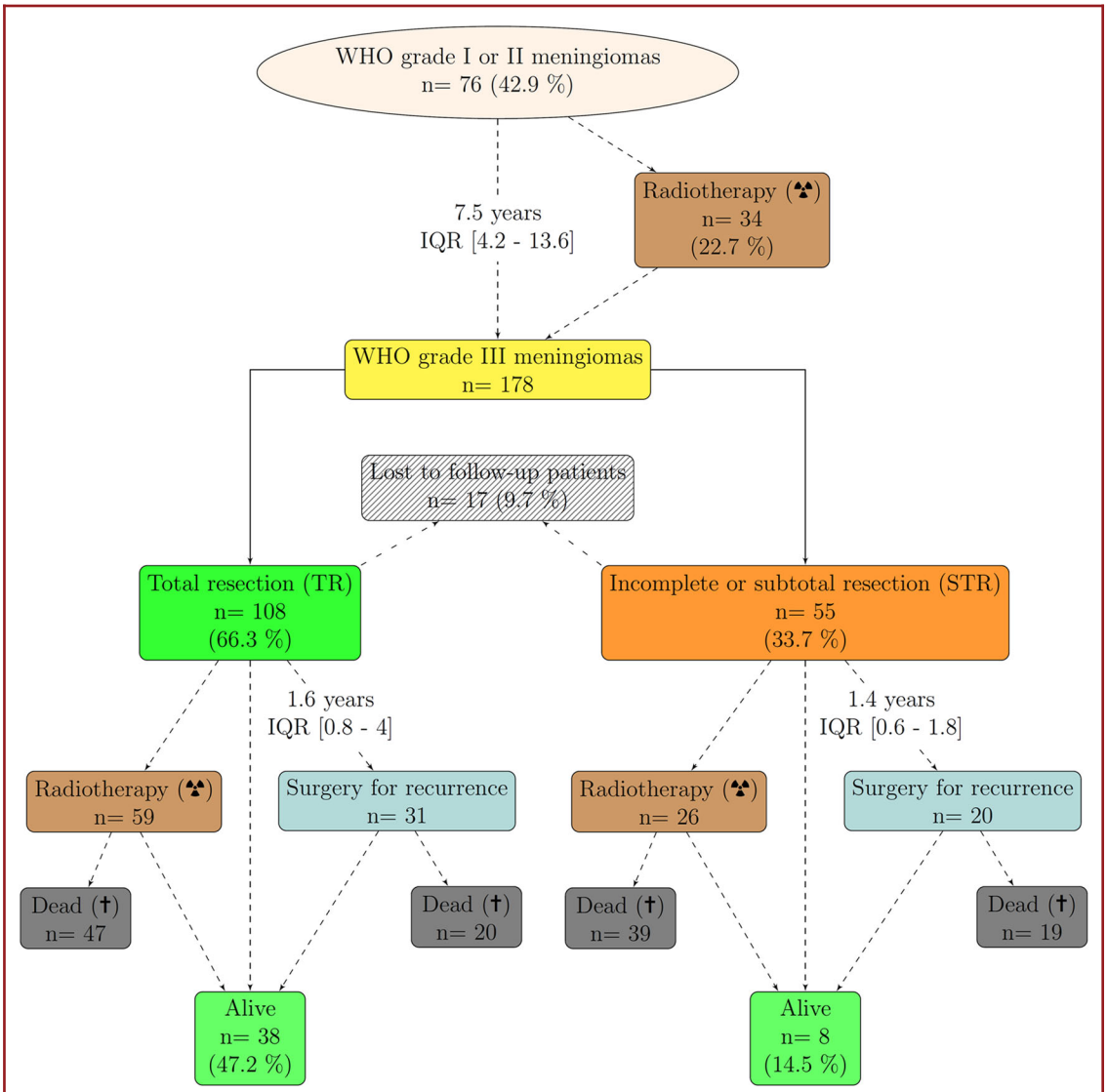


FIGURE 1. *Diagram of MM treatment and evolution. Note: The numbers may not add up correctly due to scattered loss to follow-up subjects and missing data among the different subgroups.*

differences in management. Given the rarity of these tumors, there is a shortage of literature addressing the outcome, prognosis, and optimal management of patients with MMs. To our knowledge, this international multicentre study is the first of its kind. It includes a large number of patients to increase the power of analysis and attempt to reduce sources of bias.

In comparison to atypical meningioma, the WHO 2000 definition of MM is almost identical to that of the 2007 and 2016 revisions.[1,22] This granted us to include cases with a diagnosis of MM even if they were resected before 2007. Our study covered a period of more than 15 yr during which surgery and RT techniques have evolved. However, we found no survival difference between patients diagnosed and treated before vs after 2007 ($P = .122$).

Age at Diagnosis

Patients of more than 65 yr at MM surgery are likely to have a shorter survival. This finding is consistent with previous results which also delineate cut-offs of poor prognosis around 65 yr.[15,23,24]

Progressing Meningioma

Our population is heteroclite with a significant proportion (42.9%) of progressing MMs, which are likely to behave

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TABLE 2. Univariate Cox Regression for MM Overall Survival

Variable	HR [a]	[95% CI] [b]	*P*-value
Gender male	1.20	0.82, 1.74	.34
Age at surgery <65 yr	0.54	0.37, 0.79	< **.001**
Previous benign or atypical meningioma surgery	2.25	1.54, 3.3	< **.001**
WHO grading (2007 and 2016 vs 2000 and before)	0.73	0.49, 1.09	.12
Convexity vs other locations	0.96	0.65, 1.42	.83
Convexity and parafalcine vs skull base	1.21	0.73, 2.02	.46
Side (right vs left)	0.89	0.6, 1.32	.55
Venous sinus invasion (absent vs present)	0.88	0.59, 1.33	.55
Tumour volume ≤61.8 cm^3 (median)	1.50	0.68, 3.31	.31
Simpson resection grade I and II (TR) vs III, IV, and V (STR)	0.48	0.33, 0.71	< **.001**
Simpson resection grade I, II, and III (MGTR) vs IV and V	0.47	0.32, 0.69	< **.001**
Mitoses count <20	0.79	0.51, 1.23	.3
Ki-67 index ≤ 25.5% (median)	0.79	0.47, 1.33	.38
Presence of a brain invasion	1.48	0.95, 2.33	.08
Adjuvant radiotherapy given after the MM surgery	0.61	0.41, 0.92	**.02**
Chemotherapy	1.20	0.73, 1.98	.48
Reoperation for a WHO grade III meningioma recurrence	0.98	0.66, 1.44	.91
France (n = 113) vs United Kingdom (n = 65)	0.79	0.54, 1.17	.24
By center (n = 6)	0.88	0.77, 1.02	.1

[a] Hazard ratio.
[b] 95% Confidence interval.
The **bold *P*-value** underlines the statistically significant outcome measure (HR).

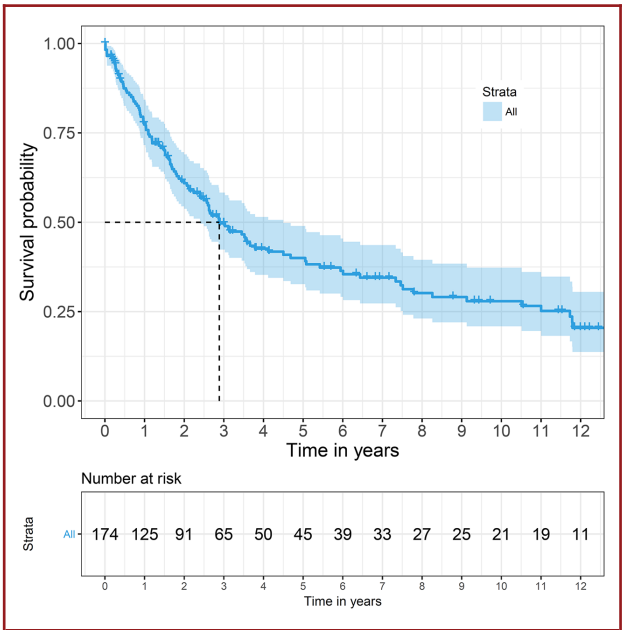


FIGURE 2. *Overall survival of patients operated on for a MM.*

differently to de novo tumors. Moreover, patients with secondary MM differ from patients with primary MM as they have already undergone at least 1 surgery and in some cases RT. However, we chose to keep secondary MM in order to minimize any selection bias and to present the data in an intention to treat framework. Patients with secondary MM have a shorter survival ($P = .004$).[25] This study confirmed the better prognosis of de novo MM. Our findings of median survival and the adverse impact of secondary MM are in keeping with those of Peyre et al[26] (2.9 vs 2.6 yr). Zhao et al[19] found that patients with a secondary tumor had a shorter progression-free survival than those with a primary MM, but did not establish a significant effect on overall survival. In common with other intracranial neoplasms such as gliomas, meningioma histopathological features may evolve and are not fixed. As only some tumors undergo aggressive transformation, there may be genetical susceptibilities or other factors influencing this mutation.[27,28] Therefore, we suggest that de novo and progressing MM should not be put together in future reports but studied apart when assessing their outcome and predictors.

Surgery

Resection of MM may be trickier compared to other grades because of their tendency to invasion. None the less, a Simpson grade I resection can still be achievable for tumor located on the convexity. A complete resection is generally more difficult to reach for meningioma infiltrating nervous or vascular structures. For all grades of meningioma, extent of resection has been shown to affect survival and is certainly the most powerful factor affecting both progression-free and overall survival.[21,29,30] Simpson's original publication defined grade III as follows: a macroscopically complete removal of the intradural tumor,

TABLE 3. Multivariable Cox Regression for MM Overall Survival

Variable	HR [a]	[95% CI] [b]	*P*-value
Age at surgery <65 yr	0.44	0.29, 0.67	< **.001**
Previous benign or atypical meningioma surgery	1.90	1.23, 2.92	**.0038**
Simpson resection grade I and II (TR) vs III, IV, and V (STR)	0.51	0.34, 0.78	**.0016**
Adjuvant radiotherapy given after the MM surgery	0.64	0.42, 0.98	**.039**

[a]Hazard Ratio.
[b]95% Confidence Interval.
The **bold *P*-value** underlines the statistically significant outcome measure (HR).

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without resection or coagulation of its dural attachment, or alternatively, of its extradural extensions, eg, an invaded sinus or hyperostotic bone.[7] Thus, grade III resection may leave some (malignant) tumor in place. We decided to focus our work on completely removed tumors rather than on gross total resection (GTR). However, removing the Simpson grade III resection cases did not affect the outcomes, either in the univariate (Table 2) or the adjusted regression analyses. Nonetheless, according to Sughrue et al,[21] it is not clear which level of resection should be attempted beyond Simpson grade II for MM.[21]

MM tends to invade the pia mater, particularly when they relapse. Large areas of cortical invasion can challenge a redo resection.[2] Although we could not confirm this fact, redo surgery may be an effective treatment for recurrence in selected cases. Redo surgery is associated with significant neurological risks.[5,21]

Radiotherapy

No clinical trial validating the effectiveness of RT has been achieved. Reported results suggest that patients may live longer after adjuvant RT.[5,29] Our results support such an association, notably in the multivariable analysis, ie, when adjusted for other prognostic factors. However, this predictor among others has the lowest level of significance in univariable and multivariable analyses. In Figure 3D, the survival curves converged around 7.75 yr, which lead us to hypothesize that in most cases, adjuvant RT may delay a fatal recurrence but does not prevent it. Moreover, there is a statistical interaction between the grade at first surgery and RT (Wald test *P*-value = .020), suggesting that RT may have a different impact on overall survival according to the grade at first surgery.

According to Kaur et al,[6] median 5-yr overall survival after radiotherapy was 55.6% and reported rates ranged from 27% to 80.8%. However, given the lack of a nonirradiated control group in most of the studies, the prognostic impact of adjuvant radiotherapy could not reliably be assessed.

Several studies have found that higher radiation doses correspond with better outcomes.[6,31] Thus, 54 or 60 Gy should be given as standard adjuvant treatment given the apparent dose–response relationship in high-grade meningiomas.[6,31]

Tumor control of MM requires high radiation doses, which are more difficult to achieve with standard 3D-conformal radiotherapy due to the tolerance doses of normal brain tissues and critical structures (such as the optic apparatus and brainstem). Therefore, modern radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) are useful options for both primary and recurrent MM. In the adjuvant setting, conventional fractionation is used rather than hypofractionated radiosurgery due to the larger volumes that usually need to be treated, with margins required to treat microscopic spread into normal brain tissue. However, hypofractionated radiosurgical techniques may be useful for treating recurrences following previous radiotherapy.[32,33] Surgical resection with the aim of achieving maximal safe resection followed by RT has been shown to improve outcomes of patients with MMs. However, close follow-up imaging is mandatory, typically immediately after surgery to confirm the surgical impression (Simpson grade), before the RT, at 3, 6, and 12 mo after the end of RT, and then every 6 mo.

Limitations

Despite its limitations, including the number of patients lost to follow-up, this study on outcome and prognostic factors affecting the survival of patients with MM is the largest reported to date. Its retrospective nature, together with the lack of clarity regarding treatment rationales and nonhomogenous management strategies without random assignment, needs to be considered when evaluating the results. Missing data did not interfere with the outcome as shown by the multiple imputation results that demonstrated similar effect to the original analysis (**Table, Supplemental Digital Content**).

Due to limited resources, a central neuropathology review was not feasible. The logistics of collecting, shipping, and reviewing material being both impractical and prohibitively expensive and archival tissue may not have been available in all cases.

However, our data represents the "real-world clinical scenario." A study of histopathological assessment between enrolling institutions and central review found a high concordance of 93.6% for WHO grade III meningioma.[34] Apart from Ki-67, we did not assess any potential molecular markers such as the

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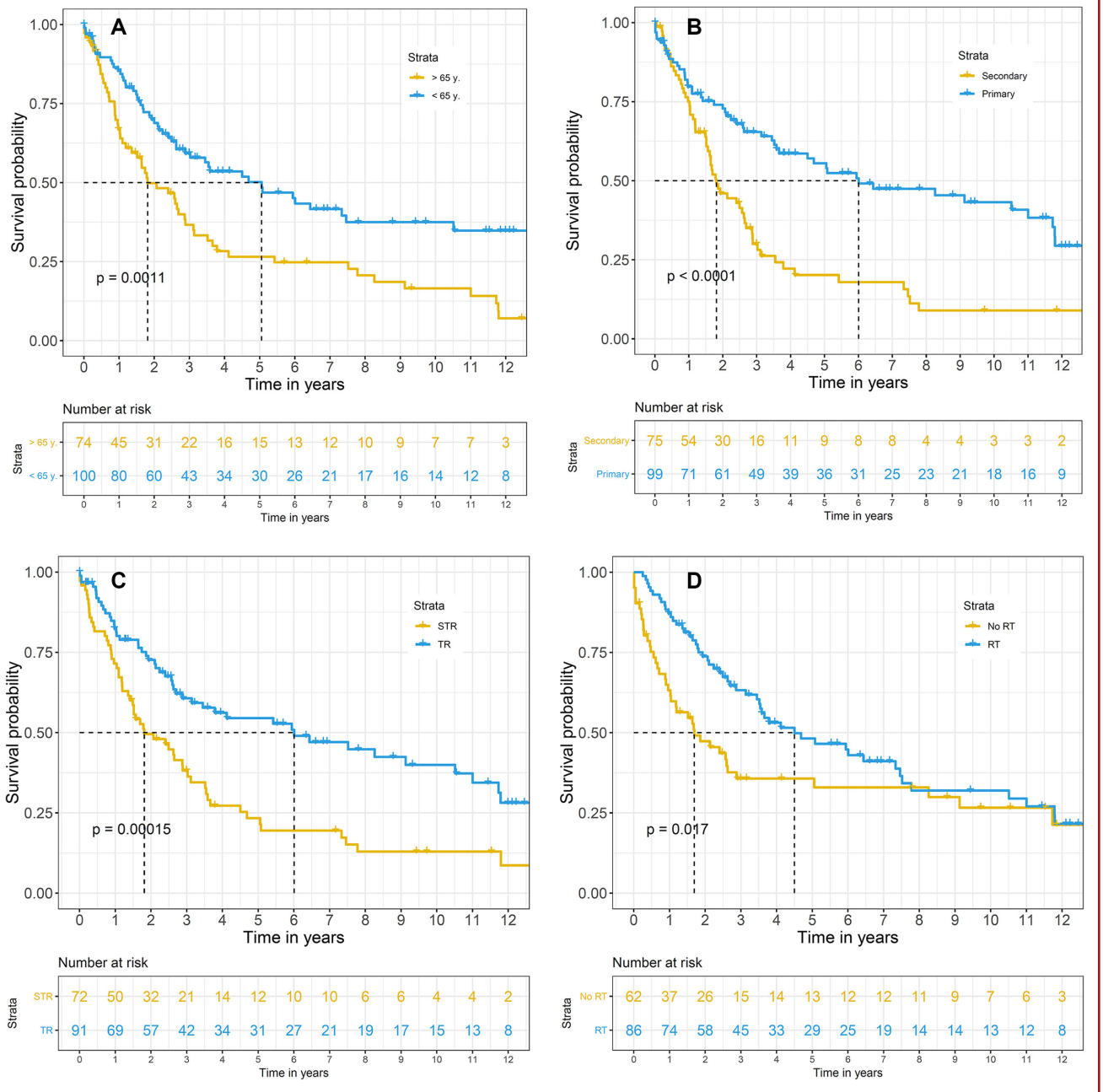


FIGURE 3. *Survival curves comparison.* **A**, *Survival by age at MM surgery.* **B**, *Survival by primary MM.* **C**, *Survival by completeness of resection.* **D**, *Survival by radiotherapy.*

prognostic value of telomerase reverse transcriptase (TERT) promoter mutation for the same reasons.[26]

We were unable to confirm some previously described predictors, such as performance status, tumor size, or location.[35] Convexity +/− parasagittal locations of MM have been described to be associated with longer survival compared to those arising from the skull base or the posterior fossa.[25] Moreover, progressing tumors are more likely located along the skull base, while primary MMs are found mainly in the convexities. While we could not confirm these statements, tumor location affects the likelihood of achieving GTR and therefore the probability of undergoing redo surgery and adjuvant RT. In patients with recurrent MM,

salvage resection, stereotactic radiosurgery, and/or chemotherapy are potential therapeutic options that may lead to extended survival. However, the benefit may decrease with successive treatments. Further studies are needed to better determine prognostic factors of this rare and heterogeneous tumor and aid in selecting optimal treatment regimens.

CONCLUSION

This large series confirms the poor prognosis associated with MM, the treatment of which remains challenging. Patients under 65-yr-old with primary MM may live longer after complete resection and postoperative radiotherapy. Even with aggressive treatments, local control remains difficult to achieve.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Table. Results after multiple imputations.

Acknowledgments

The authors thank the following people for their assistance: Prof Sebastian Brandner and Amanda Leverett, Department of Neuropathology, UCLH, London, United Kingdom; Janice Lafferty, Department of Neurosurgery, Queen

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Elizabeth University Hospital, Glasgow, Scotland; Dr Andres Kulla, Elizabeth Fraser, and Jacqueline MacPherson, Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow, Scotland; Melissa McEwan, Radiotherapy Department, The Beatson West of Scotland Cancer Centre, Glasgow, Scotland; Pr Betrand Devaux, Department of neurosurgery, Sainte Anne Hospital, Paris, France; Dr Sebastien Freppel, Department of Neurosurgery, Sud Réunion Hospital, 97410 Saint-Pierre, France; Dr Guillaume Chotard, Department of Neuropathology, Pellegrin Hospital, 33076 Bordeaux, France; and all the neurosurgeons, oncologists, and pathologists at the above-mentioned institutions.

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COMMENT

The authors present an international multicenter retrospective study of malignant meningiomas. The review is prompted by the paucity of large studies (ie, >30 patients) on the topic. Their analysis of 178 patients is fairly large, and includes the various modalities employed for treatment, the histopathological grade of resected tumors, rates of recrudescence, mortality rates, and perhaps most importantly, prognostic factors identified in the sample. This manuscript posits young age (<65 years of age), extent of resection, and adjuvant therapy as positive prognostic factors in overall survival of WHO grade III meningiomas. The need for Simpson Grade I resection of these challenging neoplasms is likewise underscored and recapitulated. These steps are important in informing the standard of care in the face of a sundry of yet-unstandardized management options currently employed by neurosurgeons worldwide.

Robust and appropriate statistical analyses were performed to account for analytical biases that are inherent to such retrospective reviews of highly morbid and mortal conditions. The included tables and figures are appropriate representations of the data presented, and reflect the study's main tenants in a manner to that is readily understandable. Such a clinical review is indeed lacking, and the authors' efforts to augment existing literature on management strategies of this overall rare permutation of meningioma is commendable. The paper is a meaningful inclusion to the current literature, and supplements other very recently published data on the matter. As the authors indicate, the retrospective nature of the study as well as the heterogonous treatment strategies limits the clinical utility of the study. Future prospective studies that address these limitations should look to validate the authors' results.

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Comparison of Motor Outcome in Patients Undergoing Awake vs General Anesthesia Surgery for Brain Tumors Located Within or Adjacent to the Motor Pathways

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The methods and result sections were partially presented as an e-poster during the Society for Neuro-Oncology meeting November 16-19, 2017, San Francisco, California.

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Received, February 22, 2018.
Accepted, February 7, 2019.
Published Online, February 20, 2019.

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BACKGROUND: Surgical removal of intra-axial brain tumors aims at maximal tumor resection while preserving function. The potential benefit of awake craniotomy over craniotomy under general anesthesia (GA) for motor preservation is yet unknown.

OBJECTIVE: To compare the clinical outcomes of patients who underwent surgery for perirolandic tumors while either awake or under GA.

METHODS: Between 2004 and 2015, 1126 patients underwent surgical resection of newly diagnosed intra-axial tumors in a single institution. Data from 85 patients (44 awake, 41 GA) with full dataset who underwent resections for perirolandic tumors were retrospectively analyzed.

RESULTS: Identification of the motor cortex required significantly higher stimulation thresholds in anesthetized patients (9.1 ± 4 vs 6.2 ± 2.7 mA for awake patients, $P = .0008$). There was no group difference in the subcortical threshold for motor response used to assess the proximity of the lesion to the corticospinal (pyramidal) tract. High-grade gliomas were the most commonly treated pathology. The extent of resection and residual tumor volume were not different between groups. Postoperative motor deficits were more common in the anesthetized patients at 1 wk ($P = .046$), but no difference between the groups was detected at 3 mo. Patients in the GA group had a longer mean length of hospitalization (10.3 vs 6.7 d for the awake group, $P = .003$).

CONCLUSION: Awake craniotomy results in a better early postoperative motor outcome and shorter hospitalization compared with patients who underwent the same surgery under GA. The finding of higher cortical thresholds for the identification of the motor cortex in anesthetized patients may suggest an inhibitory effect of anesthetic agents on motor function.

KEY WORDS: Brain tumors, Awake craniotomy, Electrophysiological monitoring, Motor function

Neurosurgery 85:E470–E476, 2019 DOI:10.1093/neuros/nyz007 www.neurosurgery-online.com

Surgical removal of intra-axial brain tumors located within or adjacent to motor pathways poses a challenge for neurosurgeons. Maximal and safe resection has been shown to have a positive effect of overall survival (OS). Aiming for complete resection, however, is often countered by the risk of postoperative neurological worsening, particularly when the tumor is located adjacent to or within functional brain regions, such as the motor areas.[1] Extensive resection that extends too far into critical and eloquent structures may lead to permanent worsening of the patient's condition and compromise both quality of life and OS.[2] The surgical boundaries are often difficult to establish due to the infiltrative nature of the tumor, accompanied by edema and a mass

ABBREVIATIONS: dcMEP, direct cortical motor evoked potential; **DES,** direct electrical stimulation; **DTI,** diffusion tensor imaging; **EMG,** electromyography; **EOR,** extent of resection; **GA,** general anesthesia; **HGG,** high-grade glioma; **ISM,** intraoperative stimulation monitoring; **KPS,** Karnofsky Performance Scale; **LGG,** low-grade glioma; **LOS,** length of stay; **MRI,** magnetic resonance imaging; **OS,** overall survival; **scMEP,** subcortical motor evoked potential; **WHO,** World Health Organization

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effect that lead to distortion of the normal brain anatomy. In order to preserve motor function while maximally resecting the tumor, the procedure is usually performed with electrophysiological mapping and monitoring via intraoperative stimulation monitoring (ISM).[3] The resection can be done while the patient is under general anesthesia (GA); however, mapping of areas involving the cortical and subcortical components of the primary motor pathway can also be performed while the patient is awake. In this manner, utilizing the patient's collaboration, voluntary motor movements can be observed in a more clinical manner. Most of the recent studies demonstrated that patients who underwent awake craniotomy had a favorable neurological outcome together with maximal tumor resection compared to surgical debulking under GA.[4-6] Anesthetic agents are known to adversely affect the robustness of neurophysiological recordings that are the basis for intraoperative neuromonitoring[7]; however, the degree of the influence of GA on motor excitability following direct electrical stimulation (DES) is yet unknown. In this study, we examined the impact of DES mapping on the motor functional outcome of patients who underwent surgical resection of tumors while awake or under GA during craniotomy.

METHODS

This retrospective study was based on prospectively collected data of patients who underwent surgical resection of intra-axial tumors adjacent to motor pathways. Electrophysiological mapping and monitoring via ISM were employed. The procedures were performed in a single Neurosurgery Center between 2004 and 2015. The possibility of performing awake craniotomy was offered to all patients as the preferred approach, but patients were also given the choice of undergoing surgery under GA as an acceptable option. The study was approved by the institutional review board (approval 0228-15). Given its retrospective nature, no informed consent was required. Surgeries performed to resect tumor recurrences were excluded from the study. Overall, a total of 85 adult patients (age > 18 yr) with newly diagnosed intra-axial tumors comprised the study group. Patients were assigned to undergo craniotomy while awake or under GA by physician's choice.

Clinical Characteristics

The medical records of the study patients were reviewed to collect data on demographics, comorbidities, presenting symptoms, preoperative neurological examination, operative course, intraoperative electrophysiological mapping and monitoring values, immediate and late postoperative neurological status, length of stay (LOS), and biometric and volumetric image analysis of pre- and postoperative magnetic resonance imaging (MRI) studies. The Karnofsky Performance Scale (KPS) was used to assess preoperative and postoperative functional status. Pathology was determined according to the World Health Organization (WHO) criteria[8] by a neuropathologist. Muscle strength score on a scale of 0 to 5/5 was based on the physical examination data, and the lowest scores were recorded. Each patient's postoperative outcome within 3 mo after surgery was recorded and classified as immediate (within 7 d) and late (3 mo postoperatively) symptoms. Electrophysiological mapping and monitoring data included the minimal electrical current needed to elicit motor responses recorded from electromyography (EMG) electrodes for detection of the motor cortex (direct cortical motor evoked potential [dcMEP] threshold) or for estimation of proximity to the subcortical pyramidal structures (subcortical motor evoked potential [scMEP] threshold) as described below.

Preoperative Evaluation

The preoperative evaluation of patients considered for awake craniotomy and their intraoperative management included multiple procedures as previously reported.[5]

Anesthesia

For all awake patients, the standard regimen of administering combinations of anesthetics upon arrival to the operating room included boluses of 1 mg dormicum, 100 mcg fentanyl, and 50 mg propofol followed by drip of propofol 1 mg/kg/h and remifentanyl 0.05 μg/kg/min. All patients received scalp nerve blocks using 0.5% Marcaine with 1:200 000 epinephrine, according to the location of the planned pinning and incision site, ie, a supraorbital, temporal, or occipital nerve block with local anesthetics. Anesthesia was monitored by standard monitoring procedures and also included invasive blood pressure monitoring. Spontaneous ventilation was monitored by capnography. All patients received oxygen (3 L/min) through a nasal cannula during the operation.

Surgical Technique

The Neuronavigation system (VectorVision, Brainlab, Munich, Germany) was used to plan the extent of craniotomy with up to a 3 cm margin of cortex to ensure sufficient mapping. Neurophysiological monitoring and scMEP stimulation included multiple steps as previously reported by our group.[19]

Images Analysis

The pre- and postoperative MRI scans (1.5- to 3-mm cuts) of all patients were obtained and analyzed. Using Brainlab software (BrainLAB, Heimstetten, Germany), the tumors were volumetrically analyzed by measuring hyperintense regions on T2-weighted fluid-attenuated inversion-recovery images for low-grade tumors and on T1-weighted contrast-enhanced MR images for high-grade tumors obtained up to 1 wk prior to surgery. Each tumor was segmented manually across all slices with region of interest analysis to compute pre- and postoperative volumes in cubic centimeters. A trained neurosurgeon specializing in volumetric measurements of brain tumors, who was blinded to clinical, radiological, and operative reports, performed the radiological assessment. The residual postoperative tumor volume and extent of resection (EOR) were calculated using MR images obtained within 48 h postoperatively using the methods described by our group elsewhere (25). The EOR was calculated using the following formula: (preoperative – postoperative tumor volume)/preoperative tumor volume × 100). The volume of blood products rather than the volume of the residual tumor was confirmed by comparing T1-weighted gadolinium-enhanced and nonenhanced MRIs. Biometric measurements of the shortest distances of the motor cortex or pyramidal tracts from the tumor preoperatively, or from the resection cavity postoperatively, were performed manually.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (IBM Inc, Armonk, New York) for Windows (Microsoft Inc, Redmond, Washington). Descriptive statistics were given as mean and standard

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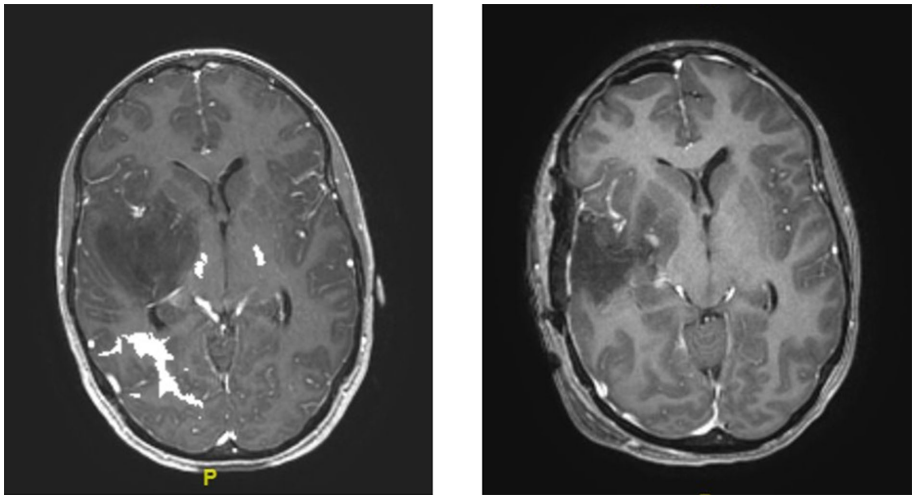


FIGURE. *Characteristic MR images of patient with LGG adjacent to the motor pathways before and after surgery.*

deviation for continuous variables, and as frequency distribution for categorical variables. The chi-square test or Fisher's exact test was used to examine group differences in categorical variables, while the 2-sample t-test was used to compare the groups for continuous variables. *P* values less than .05 were considered statistically significant.

RESULTS

Characteristics of Patients and Tumors

Eighty-five patients underwent a surgical resection of intra-axial tumors adjacent to or within the motor pathways in a single institution between 2004 and 2015. The Figure shows characteristic MR images of patient with low-grade glioma (LGG) adjacent to the motor pathways before and after surgery. The mean follow-up period was 31.6 ± 27.1 mo. Forty-four patients underwent tumor resection via awake craniotomies and they were compared to 41 patients who underwent tumor resection under GA. The patients' clinical and demographic characteristics are summarized in Table 1. The mean age of all patients was 48.7 ± 16.5 yr, with the GA group being slightly older than the awake group (mean age 50.5 ± 17.1 vs 47 ± 15.9 yr, respectively). There was a slight male predominance in both groups. All patients, except for one in the GA group, had a KPS score of >70 prior to surgery. Most of the patients had a comorbid diagnosis, including hypertension, endocrinopathies, other malignancies, or cardiac or pulmonary diseases, with a slightly higher percentage in the GA group (85.4% vs 72.7% for the awake group). The most common lesion location in both groups was the frontal lobe, followed by the parietal lobe. Most of the tumors in both groups were perirolandic (73.2% in GA vs 70.5% in the awake group, $P = .9$). There was no difference in daily steroids use between study groups. The most common pathology in both groups was high-grade gliomas (HGGs), followed by LGGs and metastases (Table 2). The awake group presents significantly more antecedent seizures (72.3% vs 31.7% for the GA group, $P = .0002$), while the GA group presented significantly more antecedent motor deficits (36.6% vs 13.6%, $P = .02$) followed by more headaches (39% vs 25%).

Intraoperative Mapping and Monitoring

In the awake patients, the minimal electrical stimulation intensity needed to evoke responses from the motor cortex (dcMEP threshold) was significantly lower than the intensity in the GA patients (6.2 ± 2.7 vs 9.1 ± 4 mA, respectively, $P = .0008$; Table 3). There was no significant group difference regarding the lowest subcortical motor threshold (min scrtMEP) used to assess the proximity of the tumor to the corticosponal tracts (9.9 ± 6.5 mA for the awake group and 12 ± 7 mA for the GA group, $P = .19$).

Tumor Resection

The postoperative outcome of the entire cohort is presented in Table 4. The mean preoperative tumor volumes were similar between the awake and GA groups (37.4 ± 28.9 vs 46.1 ± 36.5 cm^3, respectively, $P = .24$). The mean residual tumor volumes were also similar between the awake and GA groups (6.2 ± 10.1 vs 5.9 ± 9.7 cm^3, respectively, $P = .88$), as was the mean EOR (86.2% and 91.1%, respectively, $P = .17$). According to MRI and diffusion tensor imaging (DTI) analysis, the distance between the pyramidal tracts to the tumor edge prior to surgery was comparable for both groups (8.8 ± 7.2 vs 7.7 ± 7.5 mm in the awake and GA groups, respectively, $P = .48$). Similarly, based on postoperative MRI the distance between the resection cavity and the pyramidal tract was similar in both groups (10.6 ± 7.3 vs 10 ± 6.8 mm in the awake and GA groups, respectively, $P = .75$).

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TABLE 1. Demographic and Clinical Characteristic of 85 Patients Underwent a Surgical Resection of Intra-axial Tumors Within or Adjacent to Motor Pathways With Electrophysiological Monitoring 2004-2015

Characteristics	All (n = 85) n (%) Mean ± SD	Awake (n = 44) n (%) Mean ± SD	General anesthesia (n = 41) n (%) Mean ± SD	*P*-value
Age	48.7 ± 16.5	47.0 ± 15.9	50.5 ± 17.1	.33
Right dominance	76(89.4%)	38(86.4%)	38(92.7%)	.49
Male gender	51(60.0%)	27(61.4%)	24(58.5%)	.83
Preoperative KPS	94.0 ± 8.6	94.5 ± 7.3	93.4 ± 9.9	.55
Preoperative KPS > 70	84(98.8%)	44(100.0%)	40(97.6%)	.48
Comorbidity	67(78.8%)	32(72.7%)	35(85.4%)	.61
Preoperative symptoms				
Language	19(22.4%)	13(29.5%)	6(14.6%)	.12
Motor	21(24.7%)	6(13.6%)	15(36.6%)	.022
Seizures	45(52.9%)	32(72.7%)	13(31.7%)	.0002
Visual/sensory	13(15.3%)	5(11.4%)	8(19.5%)	.37
Headache, increased ICP	27(31.8%)	11(25.0%)	16(39.0%)	.24
Cognitive decline	21(24.7%)	9(20.5%)	12(29.3%)	.45
Preop muscle strength	4.7 ± 0.6	4.8 ± 0.6	4.6 ± 0.7	.18
Seizures during	3(3.5%)	2(4.5%)	1(2.4%)	1.00
AED use before surgery	44(51.8%)	27(61.4%)	17(41.5%)	.08
AED use after surgery	76(89.4%)	40(90/9%)	36(87.8%)	.73
AED type				
Dantoin	46(54.1%)	24(54.5%)	22(53.7%)	1.00
Keppra	36(42.4%)	22 (50%)	14(34.1%)	.19
Tegretol	7(8.2%)	5(11.4%)	2(4.9%)	.43
Depalept	19(8.2%)	8(18.2%)	11(26.8%)	.44
Lamictal	3(3.5%)	0	3(7.3%)	.11

AED, anti-epileptic drug; ICP, intracranial pressure; KPS, Karnofsky Performance Scale; SD, standard deviation.

Postoperative Characteristics

The immediate postoperative muscle strength was significantly lower in the GA group (4.2 ± 1.3 compared to 4.7 ± 0.9 for the awake group, $P = .046$). When dividing into groups according to tumor type, the postoperative muscle strength was still better in the awake group among HGG (4.3 vs 4.8 for GA vs awake, respectively, $P = .041$) but not for LGGs (4.6 vs 4.5 for GA vs awake respectively, $P = .14$). When combining the HGG and LGG the difference still exists (4.4 vs 4.7 for GA vs awake, respectively, $P = .044$). However, there were no longer any significant group differences in muscle strength, KPS, or late neurological complications at the 3-mo follow-up, and the most common late deficit was motor in both groups (Table 5). Notably, only 1 of the 9 patients with late motor deficit had brain metastases. Sixteen patients (18.8%) had ischemic lesions identified on postoperative MRI scans. In only 4 of the 16 patients (2 patients in each group), the ischemic lesions were associated with neurological symptoms. Three patients in each group developed systemic complications (6.8% for awake vs 7.3% for GA). Three patients from the awake group had at least 1 episode of atrial fibrillation and from the GA group, 1 patient had postoperative urinary tract infection, 1 patient had superficial vein thrombosis, and 1 had fainting episode most probably related to vasovagal syncope.

The mean LOS for the GA patients was significantly longer compared to the awake patients (10.3 vs 6.7 d, respectively, $P = .003$). The LOS was consistently shorter among awake patients in all tumor types: HGGs (7.4 vs 9.5 d, $P = .048$), LGGs (5.8 vs 8.4 d, $P = .14$), and metastases (3.7 vs 13.7 d, $P = .048$).

DISCUSSION

Surgical resections via craniotomy while the patient is awake or under GA are both acceptable approaches to treat tumors located within or adjacent to motor pathways when electrophysiological monitoring is used. It is unclear whether one approach is preferable to the other. Increasing evidence over the last 20 yr suggested that extensive tumor resection is associated with better prognosis when avoiding permanent postoperative neurological deficit. Numerous pre- and intraoperative techniques have been developed and applied over the past decades to achieve the goal of avoiding permanent postoperative neurological deficits, including functional MRI, DTI, and transcranial magnetic stimulation. Due to interindividual variance and brain shift during surgery, only intraoperative stimulation mapping could enable the creation of a patient-specific map of the brain eloquent areas and accordingly became the gold standard for safe intra-axial tumor

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TABLE 2. Tumor Characteristic of 85 Patients Underwent a Surgical Resection of Intra-axial Tumors Within or Adjacent to Motor Pathways With Electrophysiological Monitoring, 2004-2015

Characteristics	All (n = 85) n (%) Mean ± SD	Awake (n = 44) n (%) Mean ± SD	General anesthesia (n = 41) n (%) Mean ± SD	*P*-value
Tumor location				
Frontal	45(52.9%)	26(59.1%)	19(46.3%)	.28
Temporal	20(23.5)%	10(22.7%)	10(24.4%)	1.00
Parietal	30(35.3%)	13(29.5%)	17(41.5%)	.27
Insular	14(16.5%)	10(22.7%)	4(9.8%)	.15
Basal ganalia	1(1.2%)	0(0.0%)	1(2.4)	.48
Right tumor side	42(49.4%)	12(27.3%)	30(73.2%)	.00003
Tumor type				
Low-grade glioma	25(29.4%)	15(34.1%)	10(24.4%)	.25
High-grade glioma	50(58.8%)	26(59.1%)	24(58.5%)	.25
Metastases	7(8.2%)	3(6.8%)	4(9.8%)	.25
Other	3(3.5%)	0 (0.0%)	3 (7.3%)	.25
Immunohistochemistry				
Ki67	7.1 ± 7.7	6.3 ± 7.4	8.1 ± 8.1	.31
IDH1	32(37.6%)	17(38.6%)	15(36.6%)	.98
53P	41(49.4%)	20(46.5%)	21(52.5%)	.85

IDH, isocitrate dehydrogenase; SD, standard deviation.
Data are presented as n (%) or mean + SD.

TABLE 3. Intraoperative Characteristics of 85 Patients Underwent a Surgical Resection of Intra-axial Tumors Within or Adjacent to Motor Pathways With Electrophysiological Monitoring, 2004-2015

Characteristics	All (n = 85) n (%) Mean ± SD	Awake (n = 44) n (%) Mean ± SD	General anesthesia (n = 41) n (%) Mean ± SD	*P*-value
dcMEP Threshold	7.6 ± 3.7	6.2 ± 2.7	9.1 ± 4.0	.0008
Min scrtMEP	11.0 ± 6.8	9.9 ± 6.5	12.0 ± 7.0	.19
Abortion awake	0	0	0	n/a

dcMEP, direct cortical motor evoked potential; min scrtMEP, minimal subcortical motor evoked potential; SD, standard deviation.

surgery in appropriate cases. Utilizing the patient's feedback and collaboration during surgery is possible only during awake craniotomy, and the information they provide may add further safety measures to ensure the integrity of motor function. There are several intraoperative mapping and monitoring techniques used to create real-time functional monitoring of the motor areas, allowing the surgeon to define safe and functional margins of tumor resection. One technique involves the identification of the central sulcus, separating the pre- and postcentral gyri, which is presumed to be the semsorimotor border in neurologically healthy patients. This method is based upon the median nerve somatosensory evoked potential recordings of the N20 waveform representing the primary sensory cortical generator for hand area. This method is based on the concept that the N20 waveform reverses polarity when recorded across the sensorimotor border.[9-11] Localization of the primary motor cortex is achieved by applying direct cortical anodal stimulation delivered via and cortical strip electrode or a bipolar stimulator (ie, an Ojemann stimulator) and measuring the time-locked or observed motor response as recorded by EMG electrodes. Periodic or continuous subcortical stimulation using a handheld cathodal probe allows the surgeon to establish a motor threshold and in turn estimating the distance of the stimulated location to the corticospinal tracts during tumor resection.[12]

It is known that anesthetic agents inhibit certain electrophysiological parameters. Mikuni et al[13] have recently investigated the influence of the depth of anesthesia on MEP during awake craniotomy in 28 patients with brain tumors located close to the pyramidal tracts. The MEP amplitude was increased in parallel with rising bispectral index (BIS) indices, and the authors concluded that the MEP amplitude was closely correlated with the depth of anesthesia. Our cohort of patients is the largest to compare newly diagnosed brain tumor resection via a craniotomy with the patient awake or under GA and thereby provide an opportunity to assess the anesthetic effects on certain neurophysiological parameters in both groups. Similar to the findings

TABLE 4. Volumetric Analysis of Tumors of 85 Patients Underwent a Surgical Resection of Intra-axial Tumors Within or Adjacent to Motor Pathways With Electrophysiological Monitoring, 2004-2015

Characteristics	All (n = 85) n (%) Mean ± SD	Awake (n = 44) n (%) Mean ± SD	General anesthesia (n = 41) n (%) Mean ± SD	*P*-value
Preoperative tumor volume	41.7 ± 32.9	37.4 ± 28.9	46.1 ± 36.5	.24
EOR (%)	88.7 + 19.0	86.2 ± 18.4	11.8 ± 91.1	.17
GTR (%)	35 (41.2%)	18 (40.9%)	17 (41.4%)	.8
RTV	6.1 + 8.4	10.1 ± 6.2	9.7 ± 5.9	.88
Distance from PT before	8.1 + 8.6	7.7 ± 7.5	8.8 ± 7.2	.48
Distance from PT after	10.3 + 9.5	10.6 ± 7.3	10 ± 6.8	.75

EOR, extent of resection; GTR, gross total resection; RTV, residual tumor volume; PT. pyramidal tract; SD, standard deviation.

TABLE 5. Postoperative Outcome of 85 Patients Underwent a Surgical Resection of Intra-axial Tumors Within or Adjacent to Motor Pathways With Electrophysiological Monitoring, 2004-2015

Characteristics	All (n = 85) n (%) Mean ± SD	Awake (n = 44) n (%) Mean ± SD	General anesthesia (n = 41) n (%) Mean ± SD	*P*-value
Postoperative symptoms (7 d)				
Language	13(15.3%)	9(20.5%)	4(9.8%)	.23
Motor	18(21.2%)	6(13.6%)	12(29.3%)	.111
Seizures	4(4.7%)	1(2.3%)	3(7.3%)	.35
Visual/sensory	4(4.7%)	2(4.5%)	2(4.9%)	1.00
Headache, increased ICP	0(0.0%)	0(0.0%)	0(0.0%)	
Cognitive decline	4(4.7%)	1(2.3%)	3(7.3%)	.35
Infectious/hematoma	4(4.7%)	1(2.3%)	3(7.3%)	.35
Postoperative muscle strength	4.5 ± 1.2	4.7 ± 0.9	4.2 ± 1.3	.046
Postoperative symptoms follow-up 3 mo				
Language	7(8.2%)	4(9.1%)	3(7.3%)	1.00
Motor	9(10.6%)	4(9.1%)	5(12.2%)	.73
Seizures	3(3.5%)	1(2.3%)	2(4.9%)	.61
Visual/sensory	3(3.5%)	1(2.3%)	2(4.9%)	.61
Headache, increased ICP	0(0.0%)	0(0.0%)	0(0.0%)	n/a
Cognitive decline	3(3.5%)	1(2.3%)	2(2.4%)	.61
Infectious/hematoma	2(2.4%)	1(2.3%)	2(2.4%)	1.00
Postoperative KPS	95.5 ± 10.7	96.4 ± 9.4	94.6 ± 12.1	.46
Late muscle strength	4.8 ± 0.6	4.8 ± 0.7	4.7 ± 0.6	.65
Systemic complications	6(7.1%)	3(6.8%)	3(7.3%)	.34

ICP, intracranial pressure; KPS, Karnofsky Performance Scale; SD, standard deviation.

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reported by Mikuni et al,[13] the dcMEP threshold required to evoke motor responses in our awake cohort was significantly lower than in patients under GA, suggesting a cortical inhibitory effect of anesthetic agents on motor excitability. Baseline tumor characteristics and noncortical electrophysiological excitability were comparable between our awake and GA groups. For example, the distance of tumors from motor pathways before surgery was not significantly different, nor was the minimal subcortical threshold needed to elicit motor responses in either group.

The results of the current study indicate that patients who underwent awake craniotomy had better early motor function with shorter LOS compared to those who underwent surgery under GA. One possible explanation is the inhibitory effect of anesthetic agent on the brain tissue resulted in lower dcMEP threshold during surgery, required to evoke motor responses and also affect the immediate postoperative functioning. Mounting evidence suggests that anesthetic techniques that are used to keep the brain relaxed during GA, including increased rate of ventilation and the use of diuretics, may lead to vasoconstriction and hypoperfusion in the brain. Brallier et al[14] recently reported that elevated intraoperative serum lactate, a marker for hypoperfusion, in craniotomy patients under GA was associated with

new neurological deficits and longer LOS. The fact that there was no difference in late motor function between the 2 groups in our cohort of patients at 3 mo postoperatively may support the assumption that GA poses transient detrimental effect.

Reducing the LOS in hospital is an important factor in minimizing hospitalization costs. Previous comparisons between awake craniotomies and surgeries under GA have shown consistent shorter LOS for patients who underwent awake surgeries.[15-18] In the current work, the awake patients stayed 3.6 d shorter than those who were operated under GA. This discrepancy may be the result of immediate postoperative worsening in motor strength among the GA group compared to the awake group.

Limitations

The retrospective nature of this study is its main source of bias and limitation. The selection of patients for either the awake or the GA groups by the surgeon is a source for a selection bias. This bias is inherent to any retrospective analysis of awake craniotomies. However, all patients were operated in the same center, with established guidelines for decision making.

CONCLUSION

Our results show that surgical resections via awake craniotomy or with the patient under GA are both valid approaches to the treatment of brain tumors located within or adjacent to motor pathways as long as electrophysiological monitoring is used. A lower stimulation threshold to localize the motor cortex was required in awake patients, suggesting an inhibitory effect of anesthetic agents on motor function. Awake craniotomy results in a better early postoperative motor outcome and shorter LOS compared to craniotomy under GA. Our study findings suggest that awake craniotomy is a safe method for patients with intra-axial tumors within eloquent motor areas, but it remains unclear whether one approach is preferable to the other.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors investigate the potential benefit of awake-craniotomy over craniotomy under general anesthesia (GA) for motor preservation in patients undergoing surgery for perirolandic tumors while either awake (n = 44) or under GA (n = 41), with retrospective analysis of outcomes. The primary finding is that, while the extent of resection and residual tumor volume were not different between groups, awake craniotomy for rolandic and perirolandic tumors may provide advantages over craniotomies utilizing general anesthesia by decreasing length of stay, which in the authors' cases reduced from 10 to 7 days by having the patients awake. The authors feel that this discrepancy may be the result of immediate postoperative worsening in motor strength among the GA group compare to the awake group, which could be due to the inhibitory effect of anesthetic agents used during GA on brain tissue causing a transient detrimental motor effect in these patients. The authors are to be commended on their thorough study, although we must also acknowledge the importance of doing analyses like these in a multi-center manner given the considerable variability in anesthetic protocols between institutions and the variability in institutional discharge practices creating considerable variability in typical length of stays after operations like these.

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The abstract of this study has been presented as an E-Poster at the Annual meeting of the Joint Cerebrovascular Section of CNS/AANS January 22–23, 2018, Los Angeles, California.

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Received, February 10, 2018.
Accepted, January 27, 2019.
Published Online, March 20, 2019.

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Pipeline for Distal Cerebral Circulation Aneurysms

BACKGROUND: Pipeline embolization device (PED; Medtronic, Dublin, Ireland) utilization is not limited to the treatment of giant wide-necked aneurysms. It has been expanded to handle small blisters, fusiforms, and dissecting intracranial aneurysms.

OBJECTIVE: To report the use of the PED in various off-label distal cerebral circulation (DCC) arteries with a follow-up to assess clinical outcomes.

METHODS: Between 2011 and 2016, of 437 consecutive patients, 23 patients with aneurysms located in DCCs were treated with PED. Data on patient presentation, aneurysm characteristics, procedural outcomes, postoperative course, and aneurysm occlusion were gathered. To control confounding, we used multivariable logistic regression and propensity score conditioning.

RESULTS: A total of 437 patients (mean age 52.12 years; 62 women [14.2%]) underwent treatment with PED in our institution. Twenty-three of 437 (5.2%) received a pipeline in a distal artery: 11/23 middle cerebral artery, 6/23 posterior cerebral artery, 3/23 anterior cerebral artery (A1/A2, pericallosal artery), and 3/23 posterior inferior cerebellar artery. Twenty percent of the aneurysms were treated in the past, 10% had previously ruptured, and 5.9% ruptured at presentation to our hospital. The mean aneurysm size was 9.0 ± 6 mm. The mean follow-up was 12 mo (SD = 12.5). In multivariable logistic regression, no associations were found between PED deployment in DCCs and aneurysm occlusion or thromboembolic complications. PED use in DCC was associated with a good clinical outcome. Twenty-two people of 23 (95%) had a good clinical outcome in the latest follow-up.

CONCLUSION: Treatment of DCC aneurysms with PED is technically challenging mainly because of the small caliber and tortuosity of the parent arteries. The results of this study further support the safety of flow diverters in the treatment of various distal aneurysms.

KEY WORDS: Pipeline, Distal Circulation, Flow Diversion

Neurosurgery 85:E477–E484, 2019 DOI:10.1093/neuros/nyz038 www.neurosurgery-online.com

The use of pipeline embolization devices (PED™, Covidien Neurovascular, Medtronic Inc, Dublin, Ireland) in the treatment of intracranial aneurysms (IAs) has gained prominence in recent years.[1] PED was engineered to provide scaffolding for endoluminal vascular reconstruction.[2] This design diverts flow through the parent artery while promoting aneurysm thrombosis.[3] The PED design allows perforators to remain patent even in difficult arterial topography and might eliminate the need for surgery.

Currently, the PED is indicated for large and giant aneurysms (neck > 4 mm) of the internal carotid artery (ICA) between the petrous and superior hypophyseal segments, yet there are a growing number of off-label uses.[4] Among these uses are the treatment of aneurysms of irregular morphology (fusiform and dissecting), branch-point aneurysms, and small aneurysms.[5] Of particular interest is the off-label use of the PED for the treatment of distal cerebral aneurysms (DCA).[6] Critics of this use point to the difficulty in accessing distal cerebral circulations (DCCs) for successful PED placement and the relatively small caliber of distal vessels with the risk of

ABBREVIATIONS: ACA, anterior cerebral artery; **CI,** confidence interval; **DAPT,** dual antiplatelet therapy; **DCA,** distal cerebral aneurysms; **DCC,** distal cerebral circulation; **DSA,** digital subtraction angiography; **IA,** intracranial aneurysm; **ICA,** internal carotid artery; **MCA,** middle cerebral artery; **mRS,** modified Rankin Scale; **OR,** odds ratio; **PCA,** posterior cerebral artery; **PED,** pipeline embolization device; **PICA,** posterior inferior cerebellar artery

occlusion. Standard treatment techniques for DCAs include clip reconstruction, arterial bypass with aneurysm trapping, and endovascular coil-embolization. The open surgical techniques deliver high rates of occlusion but are subject to substantial risks of periprocedural and postprocedural complications with some challenges in the ability to find anatomically the parent vessel and the aneurysm, which is why often image guidance is used.[7]

Given the risks of the current treatments, the PED has the potential to improve outcomes and reduce serious complications because of its specific advantages. If the PED can be successfully deployed in a distal vessel, there may be a less risk of aneurysmal intraoperative rupture while maintaining the relative benefits of an endovascular approach of avoiding a craniotomy and providing more durability compared to the other endovascular techniques. While PED use carries its own risk of thrombus formation and jailing of perforators due to its high metal-to-surface area ratio, its comparative efficacy in the treatment of distal cerebral (DC) aneurysms requires further analysis in order to determine the relative risk.[8]

This study is a single-center preliminary evaluation of the efficacy of PED treatment in aneurysms of the DCC. We report the use of the PED in various off-label DC arteries with a follow-up to assess clinical outcomes.

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METHODS

Data of patients with aneurysms in the DCC treated at our institution with PED were retrospectively gathered. The study protocol was reviewed and acknowledged by the Institutional Review Board. All patients were consented at admission. All 23 patients treated at our referral center from 2011 to 2016 were included. Their electronic medical records were reviewed to determine the patient age, gender, history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, prior stroke, or smoking. Data on patient presentation, aneurysm morphology, treatment outcomes, postoperative complications, and aneurysm occlusion on follow-up imaging were collected for each patient (Table 1).

Prior to receiving PED therapy, all patients with an unruptured aneurysm received clopidogrel (75 mg/d) and aspirin (81 mg/d) for 10 d. Those with ruptured aneurysms were loaded with clopidogrel (600 mg) and aspirin (650 mg) 8 hr prior to PED placement. Patients allergic to clopidogrel were given prasugrel instead at a loading dose of 40 mg and a daily maintenance dose of 5 mg. Platelet function was routinely assessed via the P2Y12 assay (VerifyNow®; Accumetrics, San Diego, California) with a platelet inhibition goal of 30% to 90%. If adequate platelet inhibition was not achieved with prasugrel, ticagrelor was offered at a loading dose of 2 × 90 mg and maintenance dose of 90 mg twice daily. Intraoperatively, heparin flushes of 100 U/kg each were administered when needed to maintain the activated clotting time at 2 to 3 times the patient's baseline. Dual antiplatelet therapy (DAPT) was continued for at least 6 mo.

General endotracheal anesthesia was used in all procedures, with continuous monitoring of electroencephalography and somatosensory evoked potential. A 58Navien™ (Reverse Medical/Covidien, Medtronic) intracranial support catheter, using the triaxial guide–catheter system, was used with a Neuron™Max (Penumbra, Alameda, California) in the proximal ICA. The Navien™ was taken and advanced over the Marksman (Covidien, Medtronic) microcatheter to have maximum support. PEDs were pre-sized by measuring the inflow.

Data of a control group of 29 patients who were treated surgically or with endovascular coiling included information regarding thromboembolic or hemorrhagic events associated with the treatment, aneurysm occlusion, and the patient's functional status on the latest clinical follow-up (Table 1).

TABLE 1. Patient Characteristics

	Pipeline (Medtronic) Mean (SD)	Coiling/clipping Mean (SD)
Age (yr)	52.12 (11.85)	55.34 (13.7)
Sex*(M/F)	16/7	19/10
Aneurysm size (mm)	9.0 (6.30)	8.81 (5.93)
Hypertension	0.55 (0.50)	5.86 (0.50)
Smoking	0.52 (0.51)	0.35 (0.48)
Long-term recurrence	0.08 (0.28)	
Residual flow	0.14 (0.35)	
Hemorrhagic complication	0.06 (0.24)	0.03 (0.18)
Thromboembolism	0.17 (0.38)	0.06 (0.26)
Aneurysm thrombosis	0.07 (0.25)	
Intra-PED stenosis	0.08 (0.28)	
Stent migration	0.01 (0.1)	
mRS on latest follow-up	0.18 (0.39)	1.34 (2.40)
Post-op stay (d)	1.4 (0.90)	13.31 (6.89)

mRS, modified Rankin Scale; PED, pipeline embolization device.

Outcome Variables

The modified Rankin Scale (mRS) at follow-up, aneurysm occlusion on the latest digital subtraction angiography (DSA), and retreatment rates were defined as primary outcomes. Postprocedural thromboembolic and hemorrhagic events, and residual flow documented on follow-up DSA were all adopted as secondary outcomes.

Patient Follow-up

Patients received DAPT for a minimum of 6 mo to a year, and were scheduled to follow-up with the senior neurovascular surgeon at our institution every 3, 6, 12, 18, and 60 mo after their discharge from hospital. Aneurysm occlusion was graded in at least 2 angiographic views. Categorization was registered based on the updated Raymond–Roy occlusion classification of IAs treated with coil embolization. New or recurrent SAH or intraparenchymal bleeding was evaluated on head computed tomography scans in the case of clinical deterioration and if adjudged necessary. Electronic medical records were assessed to identify any retroperitoneal, gastrointestinal, or genitourinary tract hemorrhage.

Exposure Variables

The endovascular treatment of DCA with PEDs was the main exposure variable. Age and gender were both used for risk adjustment. Comorbidities used for risk adjustment were aneurysm size, balloon-assistance, history of SAH, previous coiling, hypertension, diabetes mellitus, smoking, and number of pipelines used in the initial procedure.

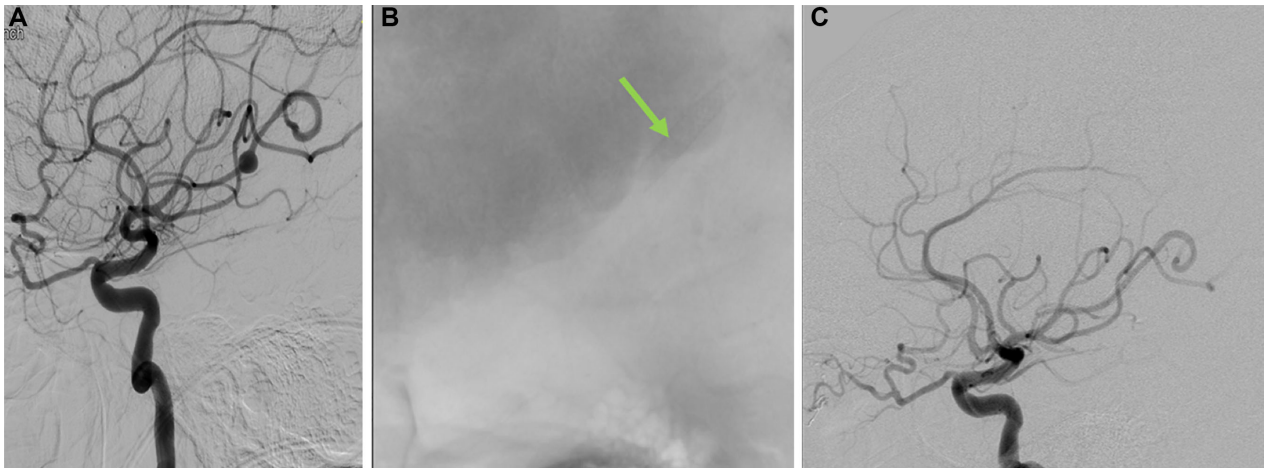


FIGURE 1. **A**, *DSA with a selective catheterization of the ICA-MCA demonstrating a saccular aneurysm at the M3 branch.* **B**, *PED (Medtronic) deployed across the neck of the aneurysm.* **C**, *Follow-up DSA showing the complete resolution of the M3 aneurysm.*

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Statistical Analysis

Continuous variables are reported as means and categorical variables as frequencies; statistical analysis was performed with the *t*-test. Statistical analysis of categorical variables was performed with χ^2. Statistical significance was considered when *P* values were <.05.

Several methods were used to address confounding in our analysis of the association of PED deployment in the DC and outcomes. Multivariable logistic and propensity score adjusted logistic regressions were used to compare binary outcomes. Mixed-effect logistic regression with the operating physician as a random-effects variable was used to control for clustering at the physician level.

A propensity score adjusted logistic regression model was also utilized to control confounding. A prediction model based on the covariates discussed above was developed and then logistic regression was performed with stratification by quantiles of the propensity score and with the surgeon as a random-effects variable.

The original analysis did not include patients who were lost to follow-up (7/437, 1.6%). Multiple imputations for those lost to follow-up were implemented in sensitivity analysis. We created 5 imputed datasets that did not show any further new associations.

All probability values were the result of two-sided tests. Stata-version-13 (StataCorp, College Station, Texas) was used for statistical analysis.

RESULTS

Patient Characteristics

Between 2011 and 2016, a total of 437 patients (mean age 52.12 yr; 62 women [14.2%]) underwent treatment with PED. Twenty-six (5.9%) patients presented with an acute SAH. Twenty-three of 437 (5.2%) received a pipeline in DCC: (11/23) middle cerebral artery (MCA; Figure 1), (6/23) posterior cerebral artery (PCA) (Figure 2), (3/23) anterior cerebral artery (ACA) (one pericallosal [Figure 3], and two at A1-segment), and (3/23) posterior inferior cerebellar artery. Smoking and hypertension were seen in 50.1% and 49.6% of our patients, respectively. The mean aneurysm size on presentation was 9.0 ± 6.3 mm (Table 2). Of the 437 aneurysms studied, 84% were saccular, 12% were fusiform, and 4% were dissecting.

Outcomes of Flow Diversion in DCC Aneurysms

Residual Flow

Of the 414 patients treated with pipeline (Medtronic), 10.8% (45/414, mean = 0.14, SD = 0.35) manifested a residual flow on the latest angiography. Of the 23 patients treated with pipeline for their DCA, 13% (3/23, mean = 0.19, SD = 0.40) had a residual flow on their latest angiography. In the multivariate-effect logistic regression, no association was found between pipeline use in DCC and residual flow on the latest angiography (odds ratio [OR], 1.60; confidence interval [CI] 95%, 0.40-6.38; *P* = .50). Similarly, in a propensity-adjusted logistic regression, pipeline use in DCC was not associated with the residual flow (OR, 1.82; CI 95%, 0.45-7.31; *P* = .39). In another multivariate-effect logistic regression, pipeline deployment in MCA aneurysms (OR, 0.67; CI 95%, 0.74-5.46; *P* = .68) and PCA (OR, 3.6; CI 95%, 0.30-43.6; *P* = .31) was not associated with the residual flow.

Thromboembolic Complications

Of the 414 patients treated with pipeline, 6.0% (25/414, mean = 0.07; SD = 0.25) vs 8.6% (2/23, mean = 0.17; SD = 0.39) of the 23 patients treated with pipeline in DCC developed thromboembolic complications. The multivariate-effect logistic regression showed no significant association between pipeline in DCC and thromboembolic events (OR,

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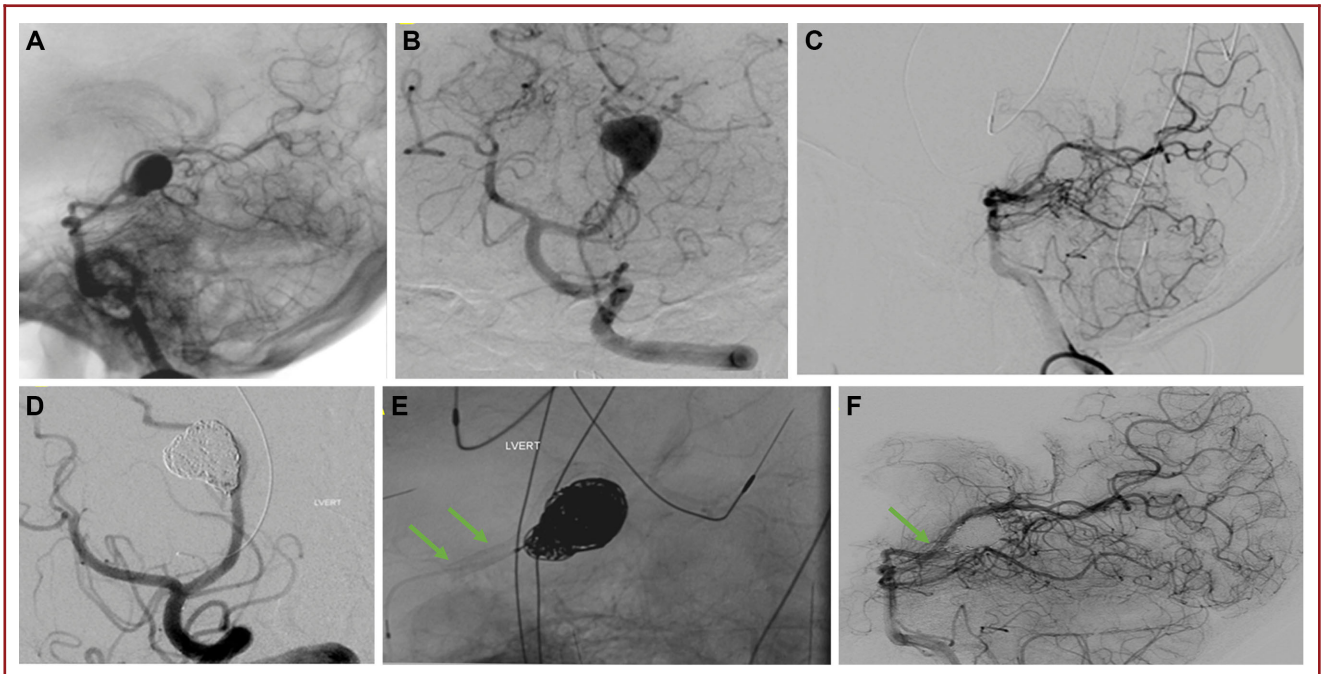


FIGURE 2. **A** *and* **B**, *DSA with a selective catheterization of the left vertebral artery (VA) showing a saccular aneurysm of the P3 segment of the left posterior cerebral artery.* **C** *and* **D**, *Complete aneurysm embolization and dome protection with pipeline assisted coiling.* **E** *and* **F**, *Six-month follow-up DSA demonstrating patent PED (Medtronic) across the neck of the coiled left P3 aneurysm with complete occlusion and isolation of the aneurysm from the parent vessel.*

1.75; CI 95%, 0.35-8.73; $P = .49$). Correspondingly, in a propensity-adjusted logistic regression, pipeline in DCC was not associated with thromboembolic events (OR, 1.86; CI 95%, 0.37-9.17; $P = .45$). In another multivariate-effect logistic regression, pipeline deployment in MCA (OR, 1.32; CI 95%, 0.15-11.81; $P = .80$) and PCA (OR, 4.36; CI 95%, 0.43-44.12; $P = .21$) aneurysms was not associated with thromboembolic events (Tables 3 and 4).

Occlusion Rate on Latest DSA

Of the 414 patients treated with pipeline, 68.3% (283/414) of the patients were Class-1 based on the Raymond–Roy classification of aneurysm occlusion, 8.7% (36/414) were Class-2, and 8.7% (36/414) were Class-3. Of the 23 patients treated with PED in DCC, 78.3% (18/23) manifested with Class-1 occlusion on latest angiography, 13% (3/23) Class-2, and 8.7% (2/23) Class-3. The multivariate-effect logistic regression showed no association between pipeline in DCC and occlusion rate on latest angiography (OR, 0.64; CI 95%, −0.26 to 0.39; $P = .70$). In the same analysis, the occlusion rate was associated with smoking ($P = .052$) and previously treated aneurysm ($P = .05$). In another multivariate-effect logistic regression, pipeline deployment in MCA (OR, −0.66; CI 95%, −0.47 to −0.34; $P = .75$) and PCA (OR, 0.28; CI 95%, −0.54 to 0.59; $P = .92$) aneurysms was not associated with aneurysm occlusion.

Clinical Outcome

Of the 414 patients treated with a pipeline, 88% had an mRS ≤ 2. Of the 23 patients treated with pipeline in DCC, 22/23 (95%) had a good clinical outcome (mRS ≤ 2); the average functional status on the latest follow-up visit was mRS = 1.0 (SD = 0.88). In multivariate analysis (OR, 0.56; CI 95%, 0.19-0.93; $P = .003$), the use of PED in DCC was associated with favorable clinical outcomes on the latest follow-up. In another multivariate-effect logistic regression, pipeline deployment in MCA (OR, 0.43; CI 95%, −0.06 to 0.92; $P = .09$) was not associated with clinical outcome on the latest follow-up. Pipeline deployment in PCA (OR, 0.69; CI 95%, 0.05-1.34; $P = .035$) was associated with favorable clinical outcomes on the latest follow-up (Tables 3 and 4).

Postprocedural Hospital Stay

Of the 414 patients treated with pipeline only, the mean postprocedural length of stay (LOS) was 1.9 d (SD = 3.0) with 64% of the patients discharged on day 1. Of 23 patients treated with pipeline in DC, the mean LOS was 1.4 d (SD = 0.9) with 70% of the patients discharged at postoperative day 1. In a multivariate-effect logistic regression, no association was found between PED in DCC with LOS (OR, −0.13; CI 95%, −1.19 to 0.94; $P = .82$). In the same multivariate regression, the postoperative stay was associated with previously treated aneurysms (OR, −0.72; CI 95%, −1.44 to −0.002; $P = .05$; Tables 3 and 4).

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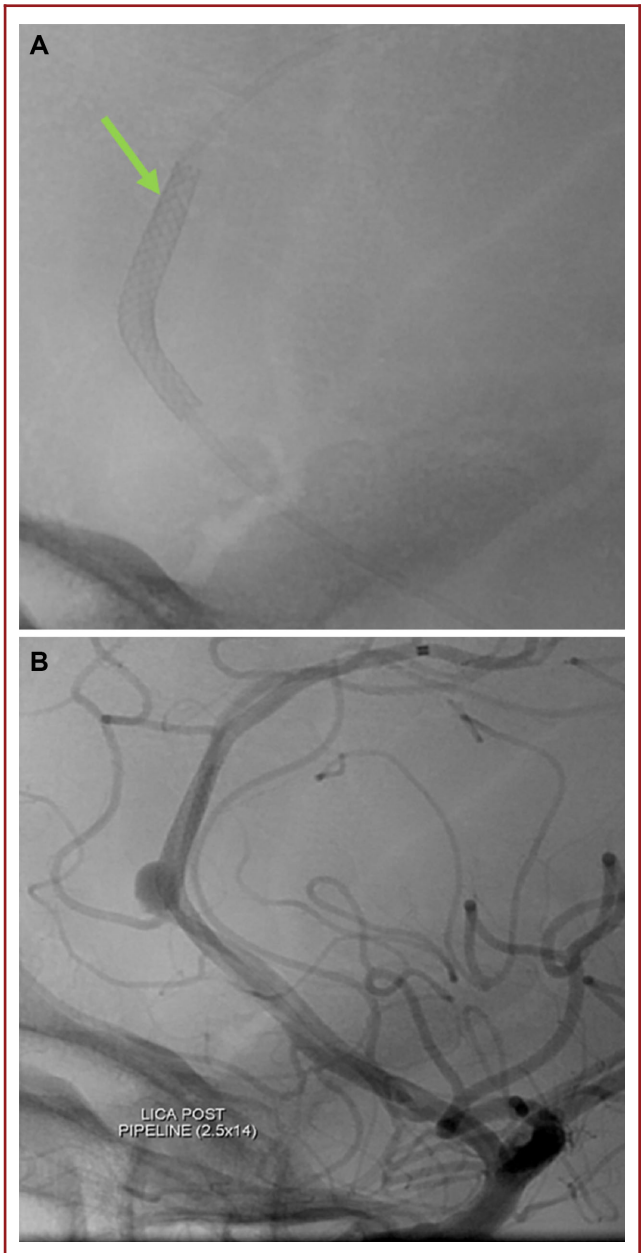


FIGURE 3. **A** *and* **B**, *DSA with a selective catheterization of the ICA-ACA revealing a PED (Medtronic) successfully deployed across the neck of a pericallosal saccular aneurysm.*

Comparison of Outcomes Between Flow Diversion and Coiling/Clipping of Distal Circulation Aneurysms

Thromboembolic Complications

Of the 29 patients treated with surgical clipping and or coiling, only 2 (6.8%) developed thromboembolic events. In the group of patients treated with pipeline in DCC, 8.6% (2/23, mean = 0.17; SD = 0.39) developed thromboembolism. The use of pipeline in DCC was not a predictor of thromboembolism, $P = .24$.

Hemorrhagic Complications

Of the 29 patients treated with surgical clipping and/or coiling, only 1 patient (3.4%) had a hemorrhagic complication. In the other group of patients who were treated with pipeline in DCC, only 1 patient had a bleeding. The use of pipeline in DCC was not associated with an increased likelihood of hemorrhagic complications, $P = .87$.

Functional Status on Long-Term Follow-up

Of the 29 patients treated with surgical clipping and/or coiling, 86.2% (25/29) had an mRS < 2 on the latest clinical follow-up (mean follow-up 24.2 mo). In the group of patients treated with pipeline for their DCAs, 22/23 (95%) had a good clinical outcome (mRS ≤ 2); the average functional status on the latest follow-up visit was mRS = 1.0 (SD = 0.88). The use of flow diversion was not associated with a worse clinical outcome on the latest clinical follow-up.

DISCUSSION

As of 2011, the use of PED (Medtronic) had been FDA approved in adults for giant and large aneurysms that extend from the petrous to the superior hypophyseal segment of the ICA.[5] The success of PED use depicted in the high aneurysm occlusion rates with an acceptable complication profile along with the increasing operator experience has led to the use of PED for a considerable variety of off-label applications.[9-14] The significant rate of recurrence of distal aneurysms treated with conventional endovascular techniques like coiling, and the high risk of complications associated with open surgery, justifies the implementation of the relatively new flow diverters for the treatment of DCC aneurysms.[7-8] The use of PED in DCC has been described in several studies, yet enough evidence to support this indication has not been extensively substantiated.[15-17]

Treatment of DCAs with PED is regarded technically challenging mainly because of the small caliber and tortuosity of their parent arteries. They also often arise at major branching points, which makes their treatment with PED less effective with a risk of occluding/narrowing of the jailed branches. Besides, perforators like the medial and lateral lenticulostriate arteries are abundant at the level of the A1-segment of the ACA and the M1-segment of the MCA, respectively, increasing the risk of perforator stroke in case they are covered with the PED.[16] Moreover, the superficial location of DCA makes them amenable to other treatment options like microsurgical clipping. This entails setting the bar high in terms of expectations and safety for the PED treatment to be at least comparable to other available treatment options. However, it is now regarded as an alternative, especially for DCAs that are deemed challenging or risky to treat with the traditional treatment methods.

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TABLE 2. Association Between Outcomes and Aneurysm in MCA

MCA[a]	OR	95% CI	*P*-value
Residual flow	0.67	0.74 to 5.46	.68
Aneurysm thrombosis	1.32	0.15 to 11.81	.80
Intra-PED stenosis	2.71	0.48 to 15.1	.25
Stent migration	26.9	1.03 to 7.04	.05
Occlusion rate	−0.66	−0.47 to −0.34	.75
mRS on latest follow-up	0.43	−0.06 to 0.92	.09
Post-op Stay	−0.21	−1.53 to 1.11	.75

CI, confidence interval; MCA, middle cerebral artery; mRS, modified Rankin Scale; OR, odds ratio; PED, pipeline embolization device.
[a]Middle cerebral artery.

TABLE 3. Association Between Outcomes and Aneurysm in PCA

PCA[a]	OR	95% CI	*P*-value
Residual flow	3.6	0.30 to 43.6	.31
Aneurysm thrombosis	4.36	0.43 to 44.12	.21
Intra-PED stenosis	2.87	0.27 to 29.54	.38
Occlusion rate	0.28	−0.54 to 0.59	.92
mRS on latest follow-up	0.69	0.05 to 1.34	.035
Post-op stay	0.69	−1.94 to 2.07	.95

CI, confidence interval; PCA, posterior cerebral artery; mRS, modified Rankin scale; OR, odds ratio; PED, pipeline embolization device.
[a]Posterior cerebral artery.

Review of Literature

A number of case reports[18-20] and retrospective studies have assessed the safety and efficacy of PED use in adults for DCAs. Some of these studies were exclusive to a specific arterial territory like the ACA,[6,21-24] MCA,[15,25-27] or PCA,[28-30] while others included aneurysms located in multiple locations.[16,17,31-34]

TABLE 4. Aneurysms Characteristics

		Aneurysm				
Age	Sex[a]	Location[b]	Size (mm)	Form[c]	Previously coiled	Concomitant pipeline-assisted coiling
65	2	MCA-M1	30.0	2	0	0
48	1	ACA-pericollosal	6.0	2	0	0
50	2	MCA-M1	15.0	1	0	0
26	1	MCA-M3	5.0	2	0	0
68	2	MCA-M1	15.0	1	0	0
56	1	MCA-M1	25.0	2	0	1
75	1	PCA-P1/P2	12.0	1	0	0
75	1	MCA-M1	6.9	1	0	0
42	2	PCA-P2/P3	13.0	3	0	1
60	2	MCA-M1	13.0	1	0	1
71	2	MCA-M1	18.0	1	0	0
68	1	PCA-P1/P2	19.0	1	0	0
68	1	MCA-M3	6.0	2	0	0
56	1	PCA-P1/P2	8.7	2	1	0
80	1	MCA-M1	16.0	1	1	0
58	1	MCA-M1	9.0	2	0	0
65	1	PCA-P1/P2	4.3	3	0	0
57	1	PCA-P1/P2	12.6	1	0	1
65	1	ACA-A1	11.0	1	1	0
50	1	ACA-A1	14.0	1	0	1
55	1	PICAA Supra-tonsillar	10.0	2	0	0
62	1	PICAA Supratonsillar	9.0	2	0	0
70	1	PICAA Anteromedullary	7.9	1	0	1

ACA, anterior cerebral artery; PCA, posterior cerebral artery; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery.
[a]Sex: 1-male; 2-female.
[b]Aneurysm location: MCA (middle cerebral artery, [M] referring to distal branch); PCA (posterior cerebral artery, [P] referring to distal branch); ACA (anterior cerebral artery, [A] referring to distal branch); PICA (posterior inferior cerebellar artery).
[c]Aneurysm form: 1-saccular; 2-fusiform; 3-dissecting.

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Relatively larger studies (>25 patients) including DCA at all locations have shown a high occlusion outcome with an acceptable complication rate. Saleme et al[17] retrospectively reviewed 32 patients with 37 DCAs at bifurcation sites that were treated with PED. All aneurysms were treated with PED alone or with concurrent coiling (18.9%). The procedural complication rate was 8% with no mortalities. At an 18 mo follow-up, 97.3% of aneurysms showed no filling, while 2.7% had an entry remnant. The authors concluded that treating DCA using PED is safe and effective when properly planned. Similarly, Lin et al[16] arrived at the same conclusion after treating 20 DCAs with PED. At an average follow-up of 7.7 mo, 77.8% of patients were found to have complete aneurysm occlusion. The complication rate was 10.7%, with no mortalities. Almost all patients had a favorable outcome (mRS 0-2) on follow-up except for one patient who had an mRS of 3. Likewise, Pistocchi et al[34] published their series of 30 DCAs treated with either silk or pipeline in 26 patients. At a mean angiographic follow-up of 13 mo, around 79% of aneurysms were totally occluded. Overall, neurological complications were deplored in 11.1% of patients, 7.4% of which were reversible. Interestingly, 21.7% of their patients were found to have clinically silent intraflow-diverter stenosis. Other studies dealt exclusively with the use of PEDs at specific distal locations. Bhogal et al[21] presented their experience in treating 26 DCAs at the level of the ACA. Only 20 patients had at least one angiographic follow-up that showed complete exclusion attained in 80% of treated aneurysms. Surprisingly, none of the covered branches in their series was occluded on follow-up. On the other hand, Yavuz et al[26] used the PED to treat 25 MCA aneurysms. According to the last follow-up, 84% of aneurysms were completely occluded.

The occlusion rate of DCA presented in the majority of smaller studies ranged between 62% and 100%, while neurologic complications ranged between 0% and 30%.[15,23,24,27,30,32,33] Very few studies reported lower occlusion rates and worse outcomes.[22,29]

Interpretation of Results

This study exhibits the largest US series of patients with DCA treated in a single institution. All studies focusing on the treatment of DCA with PEDs compared their results either to previously published articles from other institutions or to other meta-analyses. We used multivariate analysis to compare the outcome and complication rate of DCA treated as an off-label indication of the PED and carotid syphon aneurysms, also treated with PED, at the same institution. In this study, we did not find any statistically significant differences in complication rate (thrombosed aneurysm, intraflow-stent stenosis, and stent migration) between DCA and aneurysms upstream from the internal carotid bifurcation treated with the PED. Similarly, the angiographic outcome (residual flow and complete occlusion rate) was not shown to be statistically significant between the two groups. Likewise, the postprocedural hospital stay was not found to be statistically different using multivariate analysis. However, this was not the case for the clinical outcome where we found that the use of PED in the DCC was associated with the mRS on the latest follow-up. The mRS of patients with DCA treated with the PED was significantly lower than the other group. In addition, Lv et al[35] showed in their meta-analysis that only posterior circulation aneurysms and aneurysms in a peripheral location were significantly associated with increased odds of morbimortality. We found in a further multivariate-effect logistic regression analysis that the latest clinical mRS was associated with PED deployment in PCA aneurysms rather than MCA aneurysms. Nonetheless, almost all our patients had an mRS < 2 on the latest clinical follow-up.

Although a good clinical outcome (mRS < 2) of DCA treated with PED was lower than that of aneurysms located in the carotid syphon, our results (70% of patients had mRS < 2) fall in the range of good outcome achieved in published series focusing on distal aneurysms and other studies, which presented the results of treatment of IAs using PEDs.[36] We believe that treating DCA with PED is comparable in terms of complication rate and angiographic outcome with the treatment of aneurysms in a more proximal location. A proper planning and more strict patient selection would probably lead to a better clinical outcome, and this can be the focus of future studies.

Limitations

We acknowledge the high expertise of the practicing interventionists in our referral center who are exposed to an immense volume of aneurysms that they treat with PED yearly. PED in DCC should be deployed only by experienced interventionists. Treatment by inexperienced interventionists would be associated with a higher risk of complications. We have previously published, under the correspondence of our senior neurosurgeon, an article about the learning curve of our experts dealing with PED.

We believe that DCA should fall under a big spectrum, making them different from each other in many aspects (anatomy, tortuosity, and branching vessels). The small number of patients and the retrospective nature also limit our study. Larger, extensive studies with long-term follow-ups are required to further confirm the safety and efficacy of PED in off-label DCAs.

CONCLUSION

The PED is a viable option in treating DCAs. It has similar complication and occlusion rates as compared to its use in other more proximal and accessible aneurysm locations. It should be considered whenever other treatment options are pondered challenging or high risk. The main technical pearl would be to have a robust triaxial support system and to try to get the distal-access catheter being as close to the aneurysm location as possible.

Disclosures

Dr Jabbour is a consultant for Medtronic. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Tjoumakaris is a consultant for Stryker.

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Evaluating the Landscape of Clinical Research in Neurosurgery

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Received, July 10, 2018.
Accepted, January 27, 2019.
Published Online, February 27, 2019.

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BACKGROUND: Many clinical trials and observational research never reach publication in peer-reviewed journals. Unpublished research results, including neutral study findings, hinder generation of new research questions, utilize healthcare resources without benefit, and may place patients at risk without benefit.

OBJECTIVE: To examine the publication of neurosurgery trials listed in ClinicalTrials.gov.

METHODS: Clinical neurosurgery research was identified by searching the registry and categorized by study type. Associated publications were identified on Pubmed.gov.

RESULTS: Among the 709 studies identified, spine (292, 41.2%) studies were most common, followed by tumor and cranial (each 114, 16.1%). Funding was predominantly private (482, 68.0%), followed by industry (135, 19.0%) and National Institutes of Health (9, 1.3%). A lower proportion of published studies (vs unpublished) received private funding in functional (33.3 vs 65.3%) and tumor (80.0 vs 68.7%). Only 104/464 (22.4%) studies had an associated publication. The mean time from listed study completion to first publication was 31.0 ± 27.5 mo. Most published studies had significant study differences between treatment arms (n = 72, 69.2%); studies with neutral findings were less likely to be published (n = 13, 12.5%). Surgical discipline ($P = .1$), funding source ($P = .8$), patient age ($P = .4$), planned enrollment ($P = .1$), phase of trial ($P = .3$), and study type ($P = .2$) did not affect publication rates. However, the interaction between study category and funding source significantly affected publication rate ($P = .04$, generalized linear model, $R^2 = 0.05$). Publication timing (1-way analysis of variance, $P = .5$) and frequency (chi-square, $P = .2$) did not differ among disciplines.

CONCLUSION: Clinical trials and observational research in neurosurgery are often not published promptly, especially if results were nonsignificant or the trial had private funding.

KEY WORDS: Clinical research, Neurosurgery, Publication

Neurosurgery 85:E485–E493, 2019 DOI:10.1093/neuros/nyz020 www.neurosurgery-online.com

Publication of clinical trial results and observational research, including studies with neutral results, in peer-reviewed journals has an important impact on driving innovation and discovery in patient care; however, recent studies suggest that only 25 to 50% of registered clinical studies are published in peer-reviewed journals.[1-4] One definition of publication bias is the "tendency to decide to publish a study based on the results of the study, rather than on the basis of its theoretical or methodological quality."[5] Evaluation of the clinical research landscape of neurosurgery may offer insight into the prevalence of this issue in the field.

Currently, all US National Institutes of Health (NIH) clinical trials, along with most Institutional Board Review approved studies in the USA, are required to be included ClinicalTrials.gov. Chen et al[1] evaluated ClinicalTrials.gov from October 2007 through September 2010 to assess studies performed at high-volume academic medical centers (ie, those with ≥40 completed interventional trials). A total of 4347 trials across 51 studies were identified, but only 2892 (66%) of trials had disseminated results, and there was significant

ABBREVIATIONS: ANOVA, analysis of variance; **GLM,** generalized linear model; **NIH,** National Institutes of Health

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variation among medical centers. Furthermore, the proportion of studies at a given academic medical center publishing results within 24 mo of study completion ranged from 10.8 to 40.3%, suggesting poor and untimely dissemination of clinical results. Jones et al[2] evaluated 585 registered clinical trials, with a median time between study completion and publication of 60 mo. Trials with industry funding (32%) were more likely than those with nonindustry funding (18%) to be published. Ross et al[3] showed a publication rate of 46% among 635 studies from September 2005 to December 2008, with median time to publication of 23 mo. A tendency for the publication of significant study results—that is, results that achieve a desired hypothesis and show a difference between experimental arms—has also been suggested in the literature. Surgical subspecialities also suffer from publication bias, in terms of length of time until publication, favoring of significant results, and differences in publication likelihood based on funding sources.[6-11] Overall, these results suggest generally poor dissemination of results from clinical research in the peer-reviewed literature. Reasons for limited dissemination of clinical trial results have included problems with existing journals in terms of delays from submission to publication, a hesitation to publish neutral studies or negative outcomes, and strategies to present findings at scientific conferences.

Sreekrishnan et al[4] recently completed an evaluation of clinical trials in field of neurology, evaluating 2072 trials from October 2007 to July 2014, and demonstrated lower rates of publication of studies from industry sponsors (46.8%) compared with those sponsored by the NIH (54.3%). A median of 25 mo was seen between completion of studies and dissemination of results. Whereas this evaluation of published trials in neurology was recently reported, a comprehensive analysis of registered studies in neurosurgery has yet to be completed. Using the ClinicalTrials.gov database, we sought to evaluate clinical research in neurosurgery to assess whether neurosurgical studies are published at a substantial rate and how promptly. We also evaluated whether funding sources or study disciplines are correlated with publication of neurosurgery clinical studies.

METHODS

Study Sample

A Boolean search of ClinicalTrials.gov performed on June 13, 2018, for search terms "neurosurgery" OR "craniotomy" OR "burr hole" OR ("coiling AND brain aneurysm") OR ("embolization AND AVM") OR "spinal fusion" OR "discectomy" yielded 727 studies (Figure 1). Studies from any time point were included, resulting in a range from June 2, 1993, to June 8, 2018. A total of 709 studies were tabulated in the final list, which included clinical research that involved neurosurgical studies or neurological studies that included neurosurgical interventions. All excluded studies were from other medical or surgical disciplines. Institutional Board Review approval of this study of publicly available data was not required.

Clinical research variables that were evaluated as listed in ClinicalTrials.gov included trial status, study results, intervention category, trial phase, planned enrollment size, funding source, and age of trial participants. Publication of studies was identified manually by entering each trial's unique identifier, or NCT number, into Pubmed.gov to identify any published papers regarding the specific trial and their dates of publications. Studies that had a listed status of suspended or withdrawn were not included in the calculation of publication status, while studies that were listed as not yet recruiting, enroll by invitation, completed, available, recruiting, or unknown status were included if the listed trial completion date was before July 1, 2018. Time to study publication was calculated from the official start date of the trial to the date of the first published paper because the posting of trial completion dates varied, sometimes occurring after study publication. Inconsistencies in the posting of study completion dates were seen in a number of studies, that is, studies had listed completion dates after the first publication date. We used a variety of methods to evaluate publication lead time, including comparison of official start to publication time and official completion to publication time. Publications were distinguished into neutral/nonsignificant studies, significant studies, or studies publishing protocols/interim analysis. Neutral/nonsignificant studies included those without difference between control and experimental treatment arms or noninferiority trials. Significant studies were those with significant differences, whether positive or negative, for primary outcomes between control and experimental treatment arms. Interim analyses or publications of study protocols were also noted.

Statistical Analysis

Continuous results are reported as mean ± standard deviation or mean ± standard error. Discrete results are reported as numbers and % of total. Means from 2 samples were compared by the *t*-test and for multiple samples were evaluated via the 1-way analysis of variance (ANOVA) with Tukey post-hoc comparison while discrete variables were analyzed by chi-squared tests. A generalized linear model (GLM) was used to identify a main effect interaction between study disciplines and funding source on publication rates. A $P < .05$ was defined as statistically significant and analysis was completed using SPSS (V23.0, IBM, Armonk, New York).

RESULTS

A total of 709 neurosurgical studies were extracted from ClinicalTrials.gov (Table 1). The most common subspecialty was spine (292, 41.2%), followed by tumor (114, 16.1%), cranial (114, 16.1%), vascular (76, 10.7%), functional (58, 8.2%), other (53, 7.5%), and peripheral nerve (2, 0.3%). Two hundred sixty (36.7%) studies were completed. Most clinical research involved an intervention (535, 75.5%) vs an observational (174, 24.5%) aim. Most interventional trials typically involved a drug (198, 27.9%), a procedure (17, 25.0%), or a device (168, 23.7%). More than half of the studies did not describe their phase in the filing (unknown phase [175, 24.7%]; not applicable [269, 37.9%]). The proposed mean size of study enrollment was 198 ± 714 patients (range 0-12 000). Funding predominantly came from private sources (eg, universities, foundations) (482, 68.0%), followed by industry (135, 19.0%), and lastly by the NIH (9, 1.3%). Mixed funding sources were seen in 83 trials (11.7%). Most studies involved adults/older adults (528, 74.5%), while studies including any children were more limited (128, 18.0%). While ClinicalTrials.gov listed 58 (8.2%) studies as

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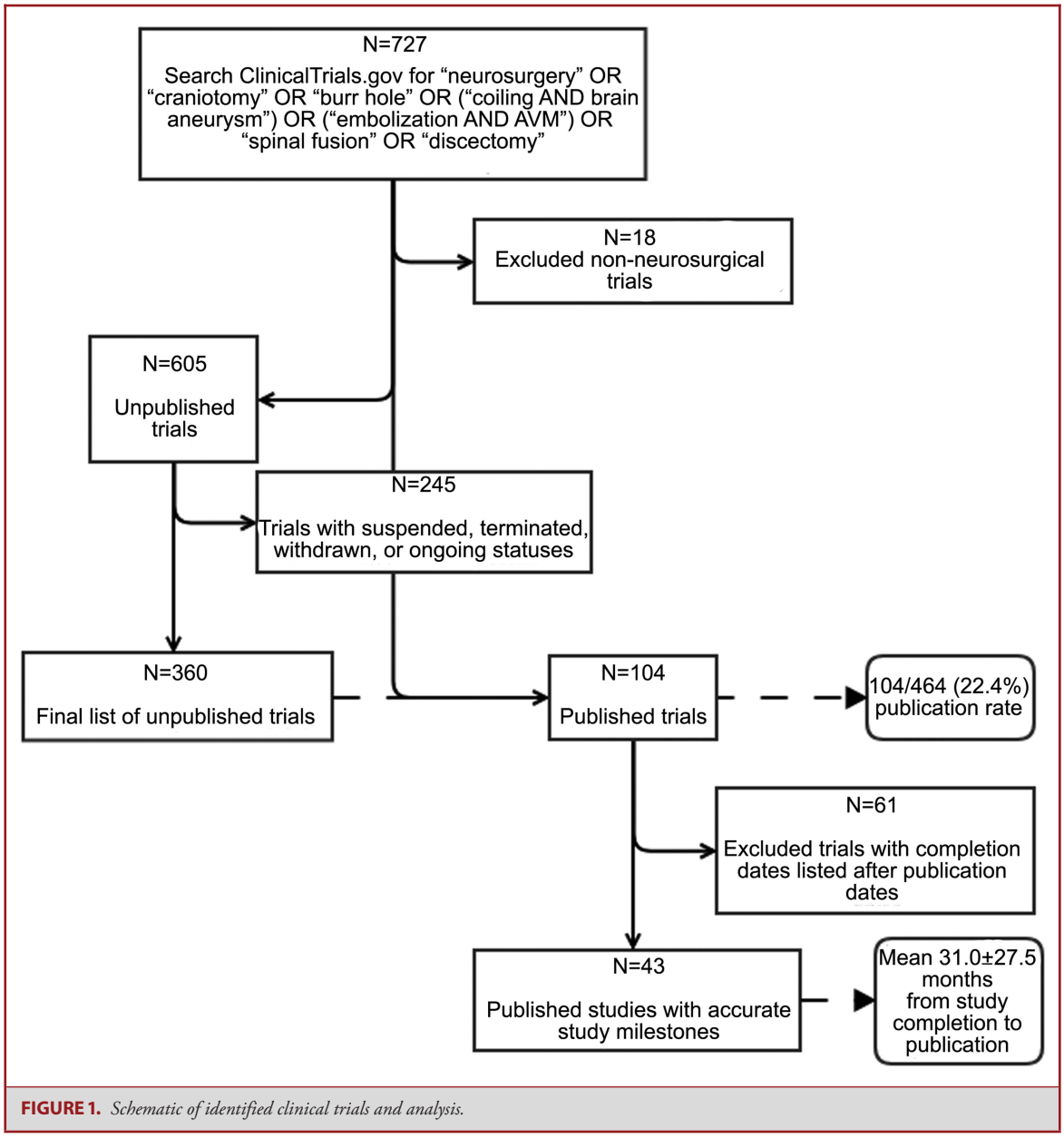


FIGURE 1. *Schematic of identified clinical trials and analysis.*

published, a total of 104 (14.7%) could be identified with some trial result on Pubmed.gov. The majority of published results were significant study findings (n = 72, 69.2%), followed by interim analysis/protocol publications (n = 19, 18.3%), and lastly neutral study results (n = 13, 12.5%). A significant difference in study intervention (Table 2) was observed (chi-square test, $P = .0001$). Cranial and tumor clinical research most often involved drugs (42.1% of each), whereas functional, spine, and vascular studies most commonly involved devices (>30% of each). In addition, clinical research funding was significantly different among study disciplines ($P = .0001$). Industry funding played a larger role in spine research (32.2%) compared with cranial (2.6%) or other (5.7%) research. NIH funding played a larger role in functional research (5.2%) than in other study disciplines. Combined funding sources were prevalent in all categories. Private funding was most prevalent in peripheral nerve (100.0%) and cranial (91.2%) disciplines and less prevalent in spine (58.6%) research. A significant interaction for study category and funding source on publication rate was seen ($P = .04$, GLM, $R^2 = 0.05$). No difference in funding distribution was seen

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TABLE 1. Characteristics of Clinical Trials in Neurosurgery

Variable	n (%); mean ± STD (range) n = 709
Discipline	
Spine	292 (41.2%)
Tumor	114 (16.1%)
Cranial	114 (16.1%)
Vascular	76 (10.7%)
Functional	58 (8.2%)
Other	53 (7.5%)
Peripheral nerve	2 (0.3%)
Status	
Completed	260 (36.7%)
Active, recruiting	184 (26.0%)
Other	71 (10.0%)
Active, not recruiting	59 (8.3%)
Not yet recruiting	43 (6.1%)
Terminated	39 (5.5%)
Withdrawn	35 (4.9%)
Enrolling by invitation	15 (2.1%)
Suspended	3 (0.4%)
Study type	
Interventional	535 (75.5%)
Observational	174 (24.5%)
Study category	
Drug	198 (27.9%)
Procedure	177 (25.0%)
Device	168 (23.7%)
Other	53 (7.5%)
Diagnostic	49 (6.8%)
Biological	24 (3.4%)
Behavioral	22 (3.1%)
Radiation	11 (1.6%)
Genetic	7 (1.0%)
Combination	1 (0.1%)
Phase	
0	6 (0.8%)
1	33 (4.7%)
1/2	26 (3.7%)
2	56 (7.9%)
2/3	11 (1.6%)
3	44 (6.2%)
4	89 (12.6%)
Unknown	175 (24.7%)
Not applicable	269 (37.9%)
Planned enrollment	198 ± 714 (0, 12 000)*
Funding	
Industry	135 (19.0%)
NIH	9 (1.3%)
Private	482 (68.0%)
Other (government)	2 (0.3%)
Mixed industry/NIH	1 (0.1%)
Mixed private/industry	61 (8.6%)
Mixed private/NIH	15 (2.1%)
Mixed private/NIH/industry	1 (0.1%)
Mixed private/NIH/government other	1 (0.1%)
Mixed private/government other	2 (0.3%)
Age group	
Adult, older adult	528 (74.5%)
Child, adult, older adult	69 (9.7%)
Child, adult	41 (5.8%)
Adult	51 (7.2%)
Child	18 (2.5%)
Older adult	2 (0.3%)
Listed as published on ClinicalTrials.gov	58 (8.2%)
Publication found on Pubmed.gov	104 (14.7%)
Time from trial start to first publication (mean ± STD), months	62.1 ± 37.3*
Time from trial start to completion (mean ± STD), months	53.5 ± 43.6*
Type of publication	
Interim analysis or protocol publication	19 (18.3%)
Neutral study[a]	13 (12.5%)
Significant study[a]	72 (69.2%)

NIH, National Institutes of Health; STD, standard deviation.

[a]Neutral studies include those without significant differences between control or experimental treatment arms and noninferiority trials. Significant studies include those with statistically significant difference between control and experimental treatment arms.

*Reported as mean ± STD (range).

for cranial, other, spine, and vascular studies. The 2 available peripheral nerve studies were unpublished and privately funded. A lower proportion of published (vs unpublished) studies received private funding in functional (3/8 [33.3%] vs 32/49 [65.3%]) and tumor (12/15 [80.0%] vs 68/99 [68.7%]) disciplines.

In calculating time from study completion to publication, there were significant inconsistencies between listed completion dates and eventual publications. The average time until publication was 62.1 ± 37.3 mo from start date (range 0.07-166.4; Figure 2A). The average time from study start to listed completion was 53.5 ± 43.6 mo (range 3.0-183.6; Figure 2B). Among the 104 clinical studies that were published, 61 (58.7%) were published prior to listed completion of the trial, 21 (20.2%) were published within 2 yr of trial completion, 19 (18.3%) were published >2 yr after trial, and 3 (2.9%) lacked completion times listed in the database (Figure 2C). After excluding 61 of 104 published studies with publication dates listed prior to study completion, a mean time from study completion to publication of 31.0 ± 27.5 mo (range 0.9-134.9, median 24.4 mo) was observed (Figure 2D). After excluding 245 of 605 unpublished studies with suspended, terminated, withdrawn, or ongoing status, an overall publication rate of 22.4% (104/464) was observed. Study publication rates of the 464 potential trials varied year by year (Figure 2E). Rates ranged from 10.3% in 2017 to 41.7% in 2011, along with multiple publications of studies with listed completion dates from 2019 to 2023. Unpublished and published studies were compared

TABLE 2. Breakdown of Study Types and Funding for Each Discipline

	Cranial n = 114	Functional n = 58	Other n = 53	Peripheral nerve n = 2	Spine n = 292	Tumor n = 114	Vascular n = 76	*P*-value
Study type								
Behavioral	6 (5.3%)	2 (3.4%)	3 (5.8%)	0 (0.0%)	9 (3.1%)	1 (0.9%)	1 (1.3%)	.0001
Biological	1 (0.9%)	2 (3.4%)	1 (1.9%)	0 (0.0%)	14 (4.8%)	6 (5.3%)	0 (0.0%)	
Combination	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	
Device	15 (13.2%)	22 (37.9%)	10 (19.2%)	0 (0.0%)	89 (30.5%)	9 (7.9%)	23 (30.3%)	
Diagnostic	6 (5.3%)	3 (5.2%)	4 (7.7%)	0 (0.0%)	21 (7.2%)	6 (5.3%)	8 (10.5%)	
Drug	48 (42.1%)	4 (6.9%)	14 (26.4%)	1 (50.0%)	70 (24.0%)	48 (42.1%)	13 (17.1%)	
Genetic	0 (0.0%)	1 (1.7%)	2 (3.8%)	0 (0.0%)	2 (0.7%)	1 (0.9%)	1 (1.3%)	
Other	7 (6.1%)	3 (5.2%)	11 (21.2%)	0 (0.0%)	14 (4.8%)	9 (7.9%)	9 (11.8%)	
Procedure	30 (26.3%)	20 (34.5%)	8 (15.4%)	1 (50.0%)	72 (24.7%)	26 (22.8%)	20 (26.3%)	
Radiation	1 (0.9%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	8 (7.0%)	0 (0.0%)	
Funding								
Industry	3 (2.6%)	9 (15.5%)	3 (5.7%)	0 (0.0%)	94 (32.2%)	10 (8.8%)	16 (21.1%)	.0001
NIH	0 (0.0%)	3 (5.2%)	1 (1.9%)	0 (0.0%)	1 (0.3%)	3 (2.6%)	1 (1.3%)	
Combination[a]	7 (6.1%)	11 (19.0%)	8 (15.1%)	0 (0.0%)	26 (8.9%)	21 (18.4%)	10 (13.2%)	
Private	104 (91.2%)	35 (60.3%)	41 (77.4%)	2 (100.0%)	171 (58.6%)	80 (70.2%)	49 (64.5%)	

NIH, National Institutes of Health.

[a]Combination funding sources included mixed industry/NIH, mixed private/industry, mixed private/NIH, mixed private/NIH/industry, mixed private/NIH/government other, mixed private/government other, and other (government).

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as a group (Table 3). No difference in study discipline ($P = .1$), study type ($P = .2$), study category ($P = .6$), age group ($P = .4$), study phase ($P = .3$), planned enrollment ($P = .2$), or study funding ($P = .8$) was observed. Expectedly, a difference in study status was observed ($P = .0001$), with unpublished studies being less likely to be completed compared with published studies (33.4 vs 55.8%).

We also compared the publication rates of the various clinical research disciplines and study types (Table 4). No significant difference in time from start to first publication (1-way ANOVA, $P = .5$), start to completion of the research (1-way ANOVA, $P = .2$), interventional vs observational study type ($P = .2$), or number of published studies (chi-square test, $P = .2$) was observed for research disciplines. No difference in study funding source was seen for published findings (results not shown, chi-squared, $P = .8$). Published studies were mostly funded by private sources (75, 72.15%), followed by industry sponsorship (17, 16.3%), mixed sources (11, 10.6%), and the NIH (1, 1.0%). Publication rates of different disciplines ranged from as low as 18.7% (34/182) for spine research to 30.0% (27/90) for cranial neurosurgery studies.

DISCUSSION

These results suggest that a very low number of studies in neurosurgery that are registered at ClinicalTrials.gov have been published (104/464, 22.4%). There was no statistically significant impact of study discipline or funding source on publication numbers or time to publication. The results of this study showing poor publication rates in neurosurgery are in contrast to higher rates of publication (25-50%) in other medical disciplines.[1-4] Sreekrishnan et al[4] recently found that 48% of clinical trials in neurology are published, which is similar to previous studies in other disciplines.[3] Sreekrishnan et al showed that funding from NIH resulted in significantly higher publication rate compared with non–NIH-funded studies (54.3% vs 40.6%, $P = .02$). They observed an average time of 26.5 ± 15.2 mo from time of trial completion to publication, but there were significant differences among study disciplines. In contrast, our results did not show a difference for publication rate based on funding source or study discipline. Interestingly, it is possible that the low rate of NIH funding of neurosurgery studies may be related to the lower publication rate, as authors lack the impetus of NIH publication directives. The higher rate of private funding (482/709, 68.0%) in neurosurgery clinical studies suggests that private foundations and universities play a large role in funding clinical trials. With limited funding available for biomedical research, these results suggest that nongovernmental and nonindustry sources of funding are critical to continuing clinical research. The bias toward publication of significant study results was also suggested in our results, with 69.2% of published studies showing significant results compared with 18.3% publishing interim analysis or protocols and only 12.5% publishing neutral study results.

Time to publication remains slow. Our study suggested that the average time until publication in neurosurgery is 31.0 ± 27.5 mo (after excluding trials with inconsistently listed trial end dates). Similarly, studies on oncology trials,[12,13] postmarket analysis

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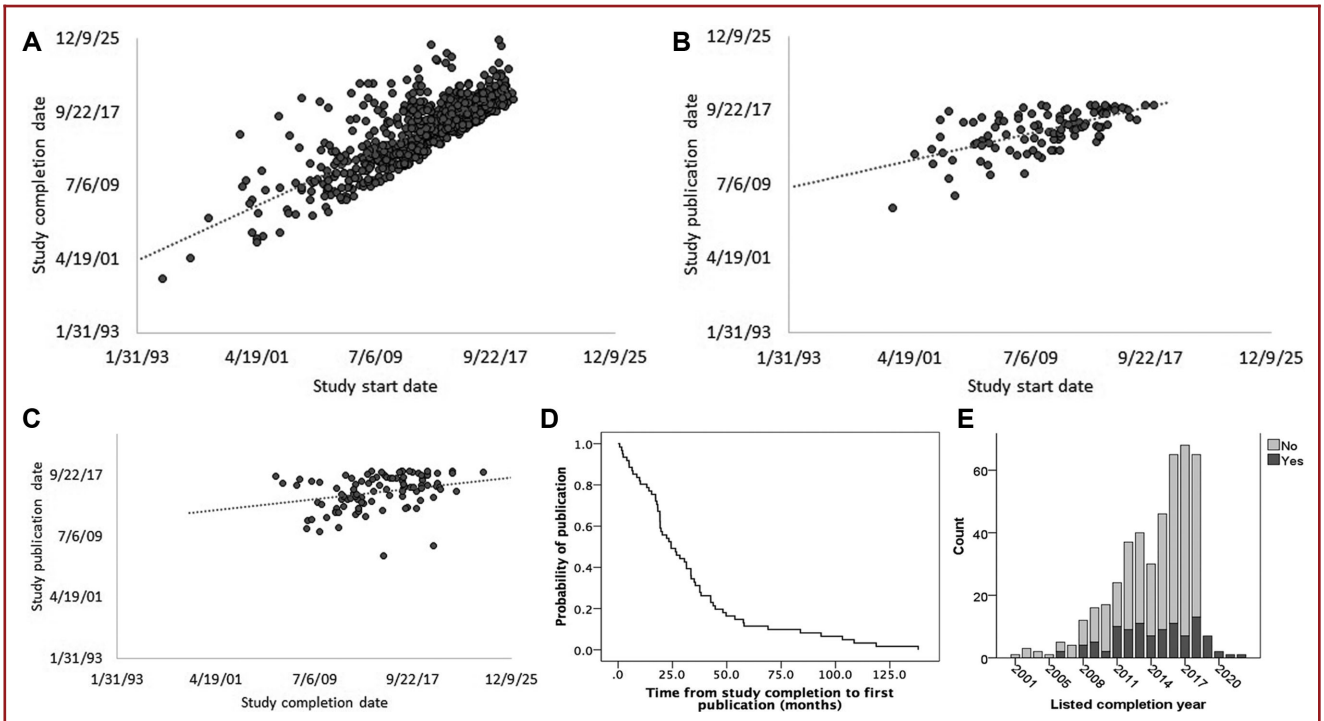


FIGURE 2. *Scatter plots of published clinical trial start, completion, and publication dates.* **A**, *Comparison of trial start and primary completion dates (including some future dates) did not show a strong correlation (r = 0.2, P = .2).* **B**, *Comparison of trial start and first publication dates showed a moderate correlation (r = 0.6, P = .0001).* **C**, *Comparison of primary completion date and first publication date did not show a strong correlation (r = 0.07, P = .5).* **D**, *A time-to-event analysis of time from trial completion to first publication (n = 43) shows a mean (± SE) time to publication of 33.5 ± 3.8 mo (median 24.4 ± 4.5 mo).* **E**, *Evaluation of publication rates for clinical trials is shown year by year and did not show a significant difference for any specific year (chi-square, P = .1).*

of medical drugs and devices,[14] and unpublished trials[2] have suggested significant delays in disseminating research. Qunaj et al[12] showed a median delay of 300 d between posting of company results regarding an oncological drug and available results for peer review, including a longer delay for neutral study results (mean 407 d). Wallach et al[14] evaluated 65 completed studies of new drugs and biologics for 106 indications with at least one postmarketing requirement; only 47 had reported results, with a mean publication time of 47 mo. Jones et al[2] evaluated 585 clinical trials across disciplines registered in ClinicalTrials.gov and found that 171 (29%) remained unpublished at a mean follow-up time of 60 mo from completion of the trial. Nonetheless, the time to publication in neurosurgery appears to be significant. The results of this delay include slowed sharing of clinical knowledge, the potential for duplication of investigation efforts, and a hindered ability for researchers to plan for future trials. Ohnmeiss[11] evaluated 263 spine-related studies using ClinicalTrials.gov and found a publication rate of 38.9% for studies listed as completed and an average time to publication of 27.9 mo. Among unpublished studies, the mean length of time that they remained unpublished was 62.0 mo at the time of the analysis. Funding sources and research type did play a role in publication rate, with funding from federal agencies or involving nonoperative care showing higher publication numbers. As with clinical trials, publications from observational studies have limitations in publication.[15,16] One report evaluating 489 observational studies showed that 39% of studies with a safety outcome had published results within 30 mo of study completion.[16] These findings reflect similar challenges in the dissemination of neurosurgery clinical research.

Our results support previous studies suggesting that improved dissemination of clinical research findings to researchers and the public are needed. Strategies to improve reporting of clinical study data and reduce publication bias have been extensively discussed.[17,18] Statements from board members of the Wellcome Trust, Medical Research Council, Cancer Research UK, Bill and Melinda Gates Foundation,[19] International Committee of Medical Journal Editors,[20] and NIH,[21] among many others, have supported improved data sharing for clinical trials. The data from some studies, although not ours, do indicate that government funding of studies and required postmarket analyses may positively influence publication rates. Our results suggest that there are potential subspecialty differences in trial publication rates. Various groups have sought to improve online

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TABLE 3. Comparison of Unpublished and Published Clinical Trials

	Unpublished (n = 605)	Published (n = 104)	*P*-value
Discipline			.1
Spine	258 (42.6%)	34 (32.7%)	
Tumor	99 (16.4%)	15 (14.4%)	
Cranial	87 (14.4%)	27 (26.0%)	
Vascular	66 (10.9%)	10 (9.6%)	
Functional	49 (8.1%)	9 (8.7%)	
Other	4 (7.3%)	9 (8.7%)	
Peripheral nerve	2 (0.3%)	0 (0.0%)	
Status			.0001
Completed	202 (33.4%)	58 (55.8%)	
Active, recruiting	166 (27.4%)	18 (17.3%)	
Other	59 (9.8%)	12 (11.5%)	
Active, not recruiting	44 (7.3%)	15 (14.4%)	
Not yet recruiting	42 (6.9%)	1 (1.0%)	
Terminated	39 (6.4%)	0 (0.0%)	
Withdrawn	35 (5.8%)	0 (0.0%)	
Enrolling by invitation	15 (2.5%)	0 (0.0%)	
Suspended	3 (0.5%)	0 (0.0%)	
Study type			.2
Interventional	449 (74.2%)	86 (82.7%)	
Observational	157 (25.8%)	18 (17.3%)	
Study category			.6
Drug	166 (27.4%)	32 (30.8%)	
Procedure	145 (24.0%)	32 (30.8%)	
Device	152 (25.1%)	16 (15.4%)	
Other	45 (7.4%)	8 (7.7%)	
Diagnostic	52 (6.9%)	6 (5.8%)	
Biological	21 (3.5%)	3 (2.9%)	
Behavioral	19 (3.1%)	3 (2.9%)	
Radiation	9 (1.5%)	2 (1.9%)	
Genetic	5 (0.8%)	2 (1.9%)	
Combination	1 (0.2%)	0 (0.0%)	
Age group			.4
Adult, older adult	447 (73.9%)	81 (77.9%)	
Child, adult, older adult	63 (10.4%)	6 (5.8%)	
Child, adult	35 (5.8%)	6 (5.8%)	
Adult	45 (7.4%)	6 (5.8%)	
Child	13 (2.1%)	5 (4.8%)	
Older adult	2 (0.3%)	0 (0.0%)	
Phases			.3
0	6 (1.0%)	0 (0.0%)	
1	28 (4.6%)	5 (4.8%)	
1/2	21 (3.5%)	5 (4.8%)	
2	44 (7.3%)	12 (11.5%)	
2/3	9 (1.5%)	2 (1.9%)	
3	34 (5.6%)	10 (9.6%)	
4	74 (12.2%)	15 (14.4%)	
Unlisted	157 (26.0%)	18 (17.3%)	
Not applicable	232 (38.3%)	37 (35.6%)	
Planned enrollment	182 ± 719	296 ± 687	.1
Funding			.8
Industry	118 (19.5%)	17 (16.3%)	
NIH	8 (1.3%)	1 (1.0%)	
Private	407 (67.3%)	75 (72.1%)	
Other (government)	2 (0.3%)	0 (0.0%)	
Mixed industry/NIH	1 (0.2%)	0 (0.0%)	
Mixed industry/private	57 (9.4%)	0 (0.0%)	
Mixed private/NIH	11 (1.8%)	4 (3.8%)	
Mixed private/NIH/industry	0 (0.0%)	1 (1.0%)	
Mixed private/NIH/government other	0 (0.0%)	1 (1.0%)	
Mixed private/government other	1 (0.2%)	1 (1.0%)	

NIH, National Institutes of Health.

requests for clinical trial data, including clinicalstudydatarequest.com and datacollaboratives.org, along with various pharmaceutical companies (eg, Pfizer, Amgen, Lilly). The ethics and financial costs of engaging patients in clinical trials also support the need to publish results in timely manner. There remain significant challenges in sharing data in an open manner, including knowledge about open data sharing services, regulatory hurdles in clinical trials, and hesitation among researchers to publish neutral studies. Further refinement of the processes to publish clinical trials may improve early dissemination of data. The importance for publication of studies, including neutral findings, in neurosurgery includes the impact on patient care and effective utilization of healthcare resources. Published knowledge can be helpful in steering future research directions and in informing public policy decisions. Perhaps one requirement of receiving NIH or other federal funding for clinical research would be to publish results in a peer-reviewed journal within a set period of time. Another strategy might be to reduce the publication burden and lead time, allowing more efficient and timely dissemination of research findings.

Limitations

One potential limitation of this study is in not capturing all research involving neurosurgical questions. Some neurosurgical studies are likely not captured with our search terms. However, the terms are broad enough that we believe the sample, if incomplete, is unbiased. Another limitation is identifying the time from study completion to publication, stemming from inconsistently entered dates into ClinicalTrials.gov. Evaluation of research only from ClinicalTrials.gov likely biases the results to reflect North American neurosurgical research but was thought to be the most objective method to identify studies since this website is publicly available and our results could be validated by other researchers. Comparison to other medical disciplines was not formally performed, which limits a final conclusion of how neurosurgical publication rates compare with those in other fields. However, this could serve as a focus of future analysis. Lastly,

TABLE 4. Breakdown of Publication Rate and Time for Study Types

	Cranial n = 90	Functional n = 37	Other n = 41	Peripheral nerve n = 2	Spine n = 182	Tumor n = 66	Vascular n = 46	*P*-value
Start to first publication (mean ± STD), months	50.3 ± 29.2	72.4 ± 44.7	61.9 ± 35.2	-	68.7 ± 40.1	63.9 ± 36.9	59.7 ± 49.3	.5
Start to completion (mean ± STD), months	28.3 ± 23.9	37.5 ± 34.4	32.2 ± 33.2	-	38.0 ± 28.9	40.7 ± 29.4	68.5 ± 54.7	.2
Interventional n (%)	68 (75.6%)	29 (78.4%)	29 (70.7%)	2 (100.0%)	139 (76.4%)	55 (83.3%)	37 (80.4%)	.2
Observational n (%)	22 (24.4%)	8 (21.6%)	12 (29.3%)	0 (0.0%)	43 (23.6%)	11 (16.7%)	9 (19.6%)	
Published n (%)	27 (30.0%)	9 (24.3%)	9 (22.0%)	-	34 (18.7%)	15 (22.7%)	10 (21.7%)	.2

STD, standard deviation.

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publication of results from conference proceedings, poster presentations, and other "gray literature" could not be linked to trial listings in all cases and do not represent peer-reviewed publication, but this may have impacted the time to the first public disclosure of study results.

CONCLUSION

Publication of clinical research in neurosurgery appears to be incomplete (22.4%) and slow (31.0 mo), potentially resulting in a delay in our ability to innovate and improve patient care. Furthermore, dissemination of results in a timely manner lags that in other medical specialties, indicating an additional emphasis on publication in neurosurgery is necessary.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We thank Kristin Kraus, MSc, for her editorial assistance.

COMMENT

This publication brings into view the low rate of publication, only 22.4%, of completed neurosurgical trials, lower than has been noted in other fields of study. The bias to publish positive results is also

emphasized. The authors bring to light the surprisingly long average time from trial end to publication of 31 months. Indirectly this then implies the need for earlier submission of results by the authors as well as publishers to minimize the time added during the revision process and the often nebulous publication lead time. Journal publication is not the only method by which information is meaningfully distributed. A major limitation of this manuscript is the lack of the ability to provide the time to first dissemination of results, eg, via verbal presentation or literature not indexed in PubMED.

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Inhibition of Manual Movements at Speech Arrest Sites in the Posterior Inferior Frontal Lobe

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Received, April 10, 2018.
Accepted, November 11, 2018.
Published Online, December 12, 2018.

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BACKGROUND: Intraoperative stimulation of the posterior inferior frontal lobe (IFL) induces speech arrest, which is often interpreted as demonstration of essential language function. However, prior reports have described "negative motor areas" in the IFL, sites where stimulation halts ongoing limb motor activity.

OBJECTIVE: To investigate the spatial and functional relationship between IFL speech arrest areas and negative motor areas (NMAs).

METHODS: In this retrospective cohort study, intraoperative stimulation mapping was performed to localize speech and motor function, as well as arrest of hand movement, hand posture, and guitar playing in a set of patients undergoing awake craniotomy for dominant hemisphere pathologies. The incidence and localization of speech arrest and motor inhibition was analyzed.

RESULTS: Eleven patients underwent intraoperative localization of speech arrest sites and inhibitory motor areas. A total of 17 speech arrest sites were identified in the dominant frontal lobe, and, of these, 5 sites (29.4%) were also identified as NMAs. Speech arrest and arrest of guitar playing was also evoked by a single IFL site in 1 subject.

CONCLUSION: Inferior frontal gyrus speech arrest sites do not function solely in speech production. These findings provide further evidence for the complexity of language organization, and suggest the need for refined mapping strategies that discern between language-specific sites and inhibitory motor areas.

KEY WORDS: Speech arrest, Brain mapping, Negative motor areas, Language organization

Neurosurgery 85:E496–E501, 2019 DOI:10.1093/neuros/nyy592 www.neurosurgery-online.com

Accumulating research indicates that the anatomical organization of language function is more complex than previously thought.[1-3] Several studies have, for example, challenged concepts surrounding the role and location of "Broca's area."[4,5] The identification of sites that elicit arrest of ongoing speech or counting has served to minimize iatrogenic language deficits.[6-10] However, stimulation of the dominant IFL has also been shown to disrupt motor functions other than speech production. For example, in awake patients, dominant IFL stimulation disturbs ongoing fine motor performance as well as repetitive movements (eg, hand or foot tapping), without eliciting responses while the patient is inactive.[11,12]

ABBREVIATIONS: IFL, inferior frontal lobe; **NMA,** negative motor areas

Numerous reports have described "negative motor areas" (NMAs), ie, cortical sites where stimulation causes arrest of ongoing motor activity.[11,13-20] NMAs were first reported in 1949 by Penfield and Rasmussen,[11] and then characterized in more detail by Lüders et al.[12,21] Stimulation of these sites elicits no response when the subject is at rest, however, during voluntary movement of the fingers, hand, foot or tongue, stimulation slows or halts the ongoing movement.[12] These sites can be effector specific (ie, only arrest hand movement) or nonspecific (stimulation results in arrest of multiple effectors). NMAs are suspected to be the ictal onset focus for negative motor seizures.[22] By incorporating evidence from functional imaging studies showing an important role for IFG in response inhibition,[23-25] Filevich and collegues[26] argued that stimulation of NMAs may lead to activation of "physiologically inhibitory pathways" involved in normal action

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control and praxis for fine movements. Given that speech production requires highly coordinated action of multiple articulators, it is possible that clinical stimulation of these physiologically inhibitory sites may also induce speech arrest.

Whether stimulation of the dominant IFL elicits speech arrest via focal disruption of a speech-specific center, or instead activates tissue involved in an inhibitory motor network (ie, NMA) is thus a question of great clinical and scientific interest. In this study, we sought to determine whether dominant IFL speech arrest sites were specific to language production, or whether they instead functioned as NMAs that also involved musculature outside the speech apparatus. Secondly, we examined the relative frequencies of speech arrest sites and negative motor sites, and characterized their spatial relationships to one another.

METHODS

Patient Population and Surgical Procedures

This retrospective study was approved by the Human Research Committee at the University of California, San Francisco. Patient consent was not required for this minimal risk study, per institutional protocol. All 11 patients underwent craniotomy with awake language and motor mapping for treatment of dominant hemisphere pathologies. The senior author (E.F.C.) performed all surgeries between May 2015 and July 2016.

Intraoperative Mapping Procedures

After exposure of the peri-Sylvian cortex and emergence from intravenous sedation (either dexmedetomidine or propofol), intravenous fentanyl was titrated for optimal balance of patient pain control and arousal during the mapping procedure. Exposed cortex was completely mapped for motor and speech function following our previously published protocol.[27,28] An Ojemann stimulator (bipolar electrodes spaced 5 mm apart) was used with the following stimulation parameters: current range 1 to 3.5 mA, pulse frequency 60 Hz, pulse width 1 ms, stimulus duration 500 to 1500 ms. Behavioral effects of stimulation on each trial were considered valid only in the absence of after-discharges or seizure activity on electrocorticography, which was monitored and reported in real time by an epileptologist. The entire mapping procedure was recorded on 2 HD video cameras–one that provided an unobstructed video of the operative field/exposed cortex, and a second that provided a detailed video of the patient's face or hand, as appropriate for different portions of the mapping procedure. Each stimulation site was registered on the patient's MRI using a neuronavigation system (BrainLab®, Westchester, Illinois), as well as with a photograph. The behavioral response corresponding to each stimulation site was recorded and later confirmed by review of the intraoperative videos.

Following completion of routine sensorimotor and speech mapping, patients were systematically stimulated to identify NMAs. Mapping for NMAs was performed anterior to the central sulcus, where they have generally been localized by previous studies.[12] Inhibitory motor area mapping was initiated at those sites where speech arrest had been elicited, if identified, and then proceeded over the surface of the exposed frontal lobe. During NMA mapping, patients were instructed to perform 2 tasks: the first task involved continuous voluntary "wiggling" of their contralateral thumb at a steady rate, while stimulation was intermittently applied. The second task involved the maintenance of contralateral finger extension (first and second digits), during which stimulation was intermittently delivered. If stimulation arrested or slowed either thumb wiggling or finger extension during more than two-thirds of the trails at a given site (ie, ceased digit movement without causing loss of tone), and induced no sensorimotor response when the patient was inactive, then that site was considered an NMA. Electrocorticography was used to ensure current spread did not explain any motor/speech arrest. In 1 patient (Patient 1), stimulation was intermittently applied while the patient played guitar with his contralateral hand, and sites that caused arrest were noted.[29]

Analysis of Mapping Results

Speech arrest sites and NMAs were plotted onto a surface reconstruction of the patients' brain which was derived from the MRI using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). The 3-dimensional coordinates were obtained using stored points from the neuronavigation, and photographs detailing their relationship to surface anatomy were used to ensure accuracy. The algorithm for warping the 3-dimensional coordinates of all the stimulation sites from the individual patients' brains into a common coordinate space for composite visualization on the MNI template brain is detailed in Hamiton et al.[30]

RESULTS

Patient Population and Surgical Procedures

Patient demographics are described in Table. The mean patient age was 43.0 ± 13.0 yr. Slightly over half of the patient population was male (6 of 11; 54.5%), and the remainder was female (5 of 11; 45.5%). Nearly all patients (10 of 11; 90.9%) presented with seizures; while 1 patient (9.1%) presented with speech disturbance. Nearly half of the patients (5 of 11; 45.5%) presented with a brain tumor (3 with grade II oligodendrogliomas, 2 with glioblastoma multiforme), 4 patients (33.3%) presented with mesial temporal sclerosis, and 2 patients (16.7%) presented with vascular malformations (1 arteriovenous malformation and 1 cavernous malformation)

Nine of 11 patients (81.8%) were right handed, and 2 patients (18.2%) were left handed. All patients underwent surgery involving the left cerebral hemisphere. Both left-handed patients underwent preoperative Wada testing or magnetoencephalography, which indicated left hemispheric language dominance.

Intraoperative Mapping Results

Positive language sites (sites where stimulation disrupted or prevented either counting, repetition, naming, or comprehension in the absence of positive motor phenomenon) were identified in 90.9% of patients (10 of 11). In each of these 10 patients, stimulation of the positive sites induced speech arrest. Additionally, stimulation elicited other speech disturbances, including anomia, perseveration, phonological errors, hypophonia, and comprehension errors. Positive motor sites (sites where stimulation elicited involuntary motor movements) were identified in 54.5% of patients (6 of 11).

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TABLE. Features of the patient population

Patient	Age (yr)	Sex	Pathology	Frontal lobe speech arrest sites	Frontal lobe motor arrest sites	Speech arrest sites that overlapped with motor arrest sites (ie, NMA)
1	27	M	Oligodendroglioma (insula)	1	1	1
2	38	F	Mesial temporal sclerosis	2	1	1
3	45	F	Mesial temporal sclerosis	2	2	1
4	27	M	Cavernous malformation (fusiform gyrus)	2	1	0
5	46	M	Mesial temporal sclerosis	2	1	0
6	50	F	Arteriovenous malformation (frontal operculum)	2	1	0
7	61	M	Glioblastoma multiforme (temporal)	1	0	0
8	27	F	Mesial temporal sclerosis	1	1	1
9	55	M	Oligodendroglioma (temporal)	2	1	1
10	35	F	Oligodendroglioma (frontal operculum)	0	0	0
11	58	M	Glioblastoma multiforme (insula)	2	0	0

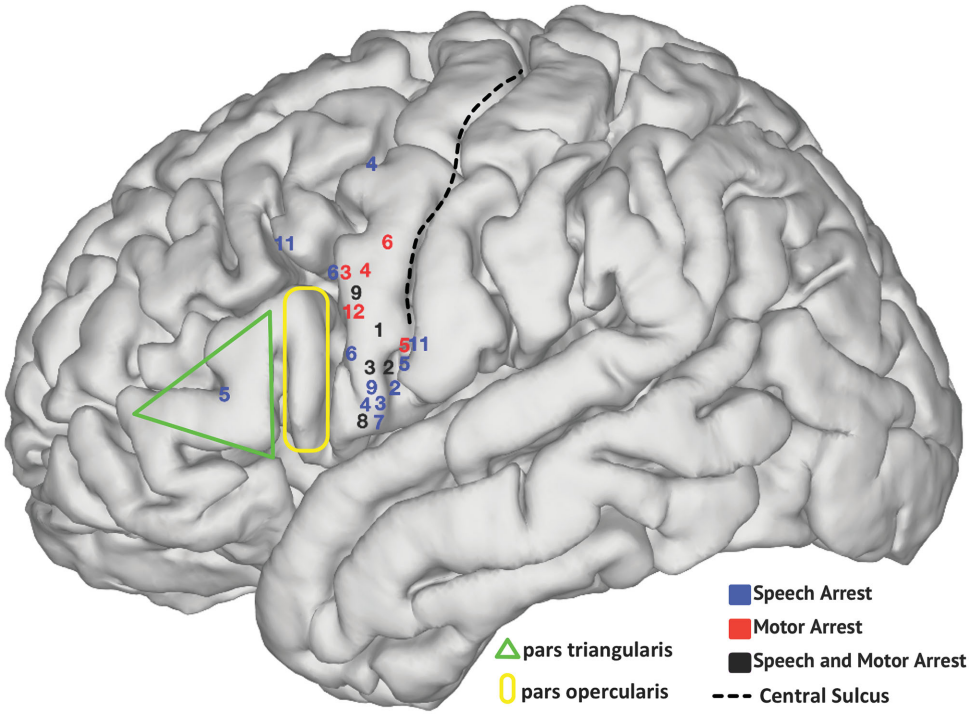
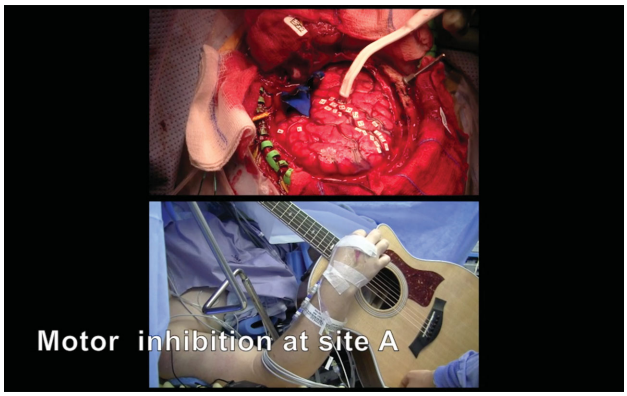


FIGURE. *Positive stimulation sites for speech arrest (blue), thumb/finger motor arrest (red), or both (black) from 11 subjects are plotted in a common left hemispheric coordinate space. Altogether, positive stimulation sites were predominantly localized to the inferior precentral gyrus. Sites are labeled by subject number.*

NMAs (sites where stimulation halted ongoing, voluntary hand movements or postures) were identified in 72.7% of patients (8 of 11). Stimulation of sites outside the IFL had no effect on the frequency or amplitude of these ongoing thumb movements. However, stimulation of specific sites in the IFL (depicted in Figure) caused the thumb movements to slow significantly, diminish in amplitude, or halt altogether. When stimulation was stopped, patients resumed the movements/postures



VIDEO. *Simultaneous video recording of the cortical surface and patient during intraoperative mapping as Patient 1 plays the guitar illustrating arrest of a complex motor task occurring when a IFL speech arrest site is stimulated.*

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that had been halted. Patients reported that during stimulation they still had intent to perform the movements but were unable to do so.

Inferior frontal lobe (IFL) stimulation also produced motor arrest in one patient who was asked to perform a complex motor task. Patient 1 was a 27-yr-old guitarist who underwent awake craniotomy for resection of a low-grade glioma from the dominant frontal operculum and insula. Preoperatively, he expressed concern that resection might impair his ability to play guitar, so stimulation intraoperative mapping was performed while the patient played guitar. First, he underwent the standard mapping procedure as described above. Then, he was given his guitar and instructed to play while cortical stimulation was carried out (Video). In the absence of brain stimulation, he played guitar without hesitation or error. However, upon stimulation of an isolated IFL site (which had caused speech arrest earlier in the mapping procedure; Figure), the patient's right-handed strumming movements were halted, and his hand remained stationary. There were no tonic contractions or abnormal postures elicited by the stimulation. When stimulation was stopped, the patient stated, "I can't play or talk." He then immediately resumed playing as before the stimulation. Repeated stimulation trials were performed, and stimulation of this IFL site elicited the same response in 4 subsequent trials.

Speech Arrest Sites are Commonly Negative Motor Areas

Across all patients, a total of 25 sites of speech arrest were identified. The majority of these sites (17 of 25; 68%) were located in the frontal lobe. A total of 9 NMAs were identified (all in the frontal lobe). The spatial distributions of speech arrest sites, NMAs, and overlapping speech/motor inhibition sites are depicted in Figure. Positive stimulation sites, regardless of type, were predominantly located in the precentral portion of the inferior frontal gyrus. Notably, 29.4% (5 of 17) frontal lobe speech arrest sites were identified as inhibitory motor sites as well. The site that caused arrest of guitar playing in Patient 1 also caused speech arrest.

In 4 of 11 patients (36.4%), distinct (ie, nonoverlapping) speech arrest and inhibitory motor sites were identified. In 3 of these 4 patients (75%), speech arrest sites were located ventral to the inhibitory motor sites (Figure).

DISCUSSION

The archetype of language organization suggests that a region of the IFL is essential for speech preparation and production. However, this concept has been challenged on 2 fronts: first, there is increasing evidence that speech function (production and perception) is widely distributed and highly networked across numerous brain regions.[1-3,31] For example, direct cortical stimulation studies have shown that the distribution of speech arrest sites is bilateral.[11,32] Second, numerous functional imaging studies suggest that portions of the IFL participate in a physiologically inhibitory network.[23-25,33-36] In this study, we focused on the relationship between stimulation sites that disrupted ongoing hand movement (ie, NMAs) and sites that caused speech arrest in the IFL. It was initially postulated that stimulation of these sites disrupted a normal neural process producing motor action.[21] However, in light of fMRI evidence that this region is activated during action inhibition, an alternate interpretation is that stimulation activates a physiologically inhibitory network important for "praxic control of fine details of action execution," albeit in a nonphysiologic way, thus arresting speech or ongoing movement.[26]

We found that speech arrest sites were not specific to speech. In 29% of cases, stimulation of speech arrest sites also caused arrest of ongoing thumb movements, as well as more complex hand movements (eg, patient 1, playing guitar). Previous studies have also demonstrated that stimulation of IFL sites can cause pure speech arrest or the arrest of additional motor effectors.[12] One possible unifying explanation of these direct cortical stimulation and neuropsychology functional imaging findings is that the historically conceptualized "Broca's area" (an IFL area that, when stimulated, causes pure speech arrest) may actually be an example of an effector-specific inhibitory motor area essential for speech praxis. Consistent with fMRI results showing activations in the IFL during stop-signal tasks where participants must inhibit an action just before it begins,[23] pure speech arrest sites show arrest of speech in both preparatory and ongoing stages.[27,28] It should be noted that, while direct cortical stimulation with bipolar (eg, Ojemann) electrodes provides a functional map of relatively high (eg, subcentimeter) resolution, it may not be able to discern between language and motor sites that are separated by small distances. We thus cannot completely exclude the possibility that NMAs identified here in fact represent 2 distinct functional sites (ie, 1 with language function and another with inhibitory motor function).

From a clinical perspective, our results suggest that speech arrest sites may be erroneously misidentified as language-specific (ie, as Broca's area) if testing of other motor effectors is not also performed. Intraoperative testing for tongue, hand, arm, or leg action inhibition can be used to differentiate speech-specific NMAs, (which may be essential for fine praxic control of speech), from nonspecific NMAs. Our results suggest that this misclassification could occur in about one-third of cases. A strong body of empiric data shows that postoperative aphasia can be avoided if speech arrest areas are preserved, making the distinction seem trivial in current clinical practice.[8,37-39] However, the observation that there are 2 types of IFL speech arrest sites–one that is speech-specific, and another that is nonspecific–leads to a clinically important question: are both of these sites essential to language function? In previous studies, resection of nonspeech NMAs has caused only transient clumsiness and no permanent motor deficits, although postoperative testing of action inhibition was not reported.[13,16,18] It remains unknown whether resection of nonspecific NMAs associated with speech arrest produces deficits similar to those that occur with resection of or injury to speech-specific NMAs. Resectability of the former, if well tolerated in terms of resultant language effects, could allow for greater extent of resection during neurosurgical procedures. Importantly, no speech arrest site, whether speech-specific or not, was resected in this study population.

Future studies should systematically test various effectors (such as arm, leg, and foot, in addition to hand) during the identification of NMAs, and, in particular, nonverbal tongue movements. In a previous study of NMAs, a mixture of both general and effector-specific inhibitory sites was described, but their distributions were not well characterized.[12] In the current study, only thumb movements were tested; whether these sites were involved in inhibition of other movements (besides those involved in speech production) is unknown. Additionally, to clarify if NMA mechanisms involve actions under preparation, future studies may vary the timing of stimulation relative to movement.[26] Given the results described here, we speculate that NMAs can inhibit effector actions at both preparatory and execution stages. Finally, the small sample size in this study limits the generalizability of our conclusions.

CONCLUSION

Evidence suggests language organization is more complex and distributed than once believed. Our results indicate IFL stimulation-induced speech arrest is not actually specific to speech: in approximately 30% of cases, stimulation of these sites also inhibited hand motor function. These findings indicate that the IFL may serve a more general role in action inhibition. Further detailed neurosurgical mapping studies, informed by contemporary speech neuroscience and the functional imaging literature, are needed in order to elucidate the complexities of speech organization and ultimately improve the sophistication of our treatment of neurosurgical patients.

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Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

This is an interesting, albeit small, series of patients that contributes to our understanding of dominant hemisphere inferior frontal lobe (IFL) language and motor function organization. The authors studied 11 patients with a variety of pathologies who were accumulated over just over 1 year, focusing on the distribution of inferior frontal speech arrest versus inhibitory motor sites. They found that ~30% (5/17) of frontal lobe speech arrest sites were also inhibitory motor sites, while 4/11 patients had distinct, non-overlapping speech arrest and inhibitory motor sites. While this paper is not particularly novel, it does increase overall knowledge of a complex area of the brain that is involved in speech production/inhibition, as well as motor inhibition. As the authors note, the mixed pathologies and relatively small number of patients limits the ability to generalize the findings. However, the study builds on past work and raises several interesting and testable questions for future investigation.

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Neurotrauma From Border Wall Jumping: 6 Years at the Mexican–American Border Wall

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Received, July 18, 2018.
Accepted, January 31, 2019.
Published Online, March 15, 2019.

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BACKGROUND: The border between the United States (US) and Mexico is an international boundary spanning 3000 km, where unauthorized crossings occur regularly. We examine patterns of neurotrauma, health care utilization, and financial costs at our level 1 trauma center incurred by patients from wall-jumping into the US.

OBJECTIVE: To determine the clinical and socioeconomic consequences from neurotrauma as a result of jumping over the US–Mexico border wall.

METHODS: Medical records of patients at (Banner University of Arizona Medical Center - Tucson) were retrospectively reviewed from January 2012 through December 2017. Demographics, clinical status, radiographic findings, treatment, length of stay, and financial data were analyzed for all patients suffering neurotrauma during that time.

RESULTS: Over 6 yr, 64 patients sustained cranial or spinal injuries directly from jumping or falling onto US soil from the border wall. Fifty (78%) suffered spinal injuries, 15 (23%) experienced cranial injury, and 1 patient had both. Total medical charges were available in 36 patients and summed $3.6 M, of which 22% was reimbursed, an amount significantly lower than expected from more conventional trauma. Neurotrauma steadily declined over the 6-yr observation period, dropping in 2017 to 6% of rates observed in 2012.

CONCLUSION: In the Southern US, neurotrauma from unauthorized border crossings occurs commonly as a result of wall-jumping. These injuries represent a clinical and costly extreme of border-related trauma, and future efforts from both sides of the border wall are needed to decrease the detrimental impacts felt both by immigrants and surrounding health care systems.

KEY WORDS: Cost analysis, Emigration and immigration, Socioeconomic factors, Spinal cord injury (SCI), Traumatic brain injury (TBI)

Neurosurgery 85:E502–E508, 2019 DOI:10.1093/neuros/nyz050 www.neurosurgery-online.com

The United States (US)–Mexico border is an international boundary spanning over 3000 km from the Pacific Ocean to the Gulf of Mexico. Estimates from 2010 cite over 350 million legal crossings, making it the most traversed border in the world.[1] However, large-scale socioeconomic differences between the countries has fueled 1.2 million unauthorized entries per year from Mexico into the US.[2] In 2006, the Secure Fence Act was passed, authorizing construction of 1125 km of high-security border fencing, intended "to prevent unlawful entry by aliens into the US and facilitate access to the international land and maritime borders by US Customs and Border Protection."[3]

Today, the barrier is still being constructed and runs, in pieces, along the US states of California, Arizona, New Mexico, and Texas. In most places, the steel barrier is 6.4 m (21 ft) tall, cemented into a 1 m (3 ft)-wide trench (Figure 1). It is composed of interrupted segments targeted toward high traffic and high-risk geography. "Virtual fencing" provided by sensors and cameras links the physical segments of the fence. Although other factors may be at play, construction of the fence has been associated with a steady decline in border apprehensions.[4,5]

ABBREVIATIONS: AGCR, adjusted gross collection rate; **ASIA,** American Spinal Injury Association; **CT,** computed tomography; **ICU,** intensive care unit; **LOS,** length of stay; **SCI,** spinal cord injury; **US,** United States

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FIGURE 1. **A**,**B**, *Two views of the wall located in the border town of Nogales, Arizona. Here it is roughly 21 feet in height and firmly constructed into above- and underground cement.*

Approximately 5000 migrant deaths have occurred along the border between 1994 and 2007.[6] No estimates are available for the number of injuries arising from illegal crossings, but morbidity is likely to be several times the mortality. All patients with injuries discovered north of the border are treated in US medical facilities, and the effect on health care resources is understandably profound.

Traumatic brain and spine injuries require the highest level of acute care and exemplify major challenges to American border state health care systems, providers, and citizens. Given the current socioeconomic and political climate of the region and the controversial border wall, the purpose of the current study was to examine patterns of neurotrauma and associated health care utilization in patients treated as a result of unauthorized border crossings at (Banner University of Arizona Medical Center - Tucson (BUMCT)), which is the only level 1 trauma center adjacent to the Arizona-Mexico border, with a catchment area extending from Yuma to San Simon.

METHODS

Medical records of patients treated at (BUMCT) from January 2012 through December 2017 were reviewed after institutional review board approval. The study design was a retrospective case review and therefore did not require consent for inclusion. Patients were identified as having jumped or fell from the border wall who sustained cranial and/or spinal trauma by obtaining history from the patient or from the accompanying Border Patrol agent. Almost all patients were discharged back into the custody of the US Border Patrol or ultimately transferred to a facility in Mexico, so follow-up was not possible in the vast majority of cases.

Demographic information, clinical presentation, radiographic findings, treatment, length of stay (LOS), and cost data were analyzed. Adjusted gross collection rate (AGCR) was calculated as the percentage of charges that were reimbursed, determined separately for both physician and inpatient hospital charges. Chi-square analysis for trend and 2-tailed *t*-tests for independent variables were performed by using Graphpad Prism software® (Graphpad Software, San Diego, California).

RESULTS

Over the 6-yr study period, we evaluated 64 patients with cranial and/or spine trauma sustained during unauthorized entry into the US. All patients were injured as a result of jumping from the border wall and were otherwise excluded. Thirty six were male (M: F, 4:3). The average age was 35 yr (range 14-63; Table 1).

TABLE 1. Basic Demographics and Hospital Data

	All	Spine	Intracranial
n	64[a]	50	15
Age	34.8	34.4	29.4
Sex (M:F)	1.3	1.2	1.5
Ethnicity			
Latin American	60	–	–
Eastern Indian	3	–	–
Asian	1	–	–
LOS (days)	5.9	4.9	8.8[b]
Surgeries	24	20	4
Discharge status			
Equivalent to home	47	35	13
Foreign hospital	7	6	1
In-patient rehab/SNF	10	9	1

SNF, skilled nursing facility; LOS, length of stay.
Basic demographics of all 63 patients. Four patients were not of Latin American ethnicity, as 3 were of Eastern Indian descent, and 1 was from China. The only statistically significant difference between brain and spine patients was LOS.
[a]There was 1 patient with both intracranial and spine injuries.
[b]Statistically significant ($P < .05$).

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All were Latin-American, except 3 people from East India and 1 person from China.

Fifty patients were diagnosed with a spine injury (78%). Burst fractures were the most common fracture and seen in 22 patients. Compression fractures were next with 13 fractures in 12 patients. There were 5 patients with superior end plate fractures without obvious compression of the vertebral body. Almost all burst and compression fractures were present in the lumbar spine. Twenty of 50 patients (40%) with a spine injury underwent surgical stabilization (6 required spinal canal decompression) spanning a total of 58 vertebral instrumented segments. There were 19 surgeries of the thoracolumbar region and 1 C6-7 anterior cervical discectomy and fusion. The average LOS for patients suffering spinal column trauma was 5 d.

Five patients suffered acute spinal cord injury (SCI), 3 American Spinal Injury Association (ASIA) A and 2 ASIA D SCI, with an average LOS of 10 d, which was significantly longer than those without SCI ($P < .01$).

Fifteen of 64 (23%) patients suffered cranial trauma (1 patient had both traumatic brain injury [TBI] and a spine fracture). Of these, 13 presented with intracranial hemorrhage and TBI (87%). There were 9 uncomplicated skull fractures (60%). One case of asymptomatic traumatic intracranial internal carotid artery dissection was identified in association with a basal skull fracture. Three patients with intracranial injury (20%) underwent a total of 4 neurosurgical procedures. One patient required a decompressive hemicraniectomy and placement of an intraparenchymal intracranial pressure monitor, another required a craniotomy for evacuation of an epidural hematoma, and a third received a extraventricular drain. The average LOS for patients with head injury was 9 d, significantly longer than those with spinal column injuries ($P < .05$).

Forty seven of 64 patients (73%) were discharged in normal or near-normal condition to the equivalent disposition of "home" back into the custody of the US Border Patrol or more rarely on their own recognizance. Ten patients (16%) were transferred to a Mexican inpatient rehabilitation or nursing facility. Seven patients (11%) were transferred directly to a Mexican acute care hospital for ongoing treatment. We observed no deaths for patients who initially survived their fall. In terms of cranial vs spine injuries, there was no significant difference between age, gender, and comorbidity. Further, there was no significant difference between these parameters and those that eventually underwent surgery.

We observed a bimodal distribution in fall frequency throughout the calendar year. The highest incidence of injury occurred in March, followed by a second peak in November, corresponding to the more temperate desert weather of spring and fall (Figure 2). However, perhaps more notable was that through the 6-yr study period, there was a consistent and statistically significant decrease in total injuries each year ($P < .001$). In 2012, there were 17 cases, which gradually fell to just 1 in 2017. There was an average decline in neurotrauma of 29% per year, resulting in a 94% overall reduction of brain and spinal injuries in 2017 compared to the index incidence of 2012 (Figure 3).

Cost Analysis

Reimbursement data for physician providers were complete for 60 patients (Table 2). Physician provider charges across all specialties totaled $672 075 for all patient encounters and were reimbursed a total of $149 292 for an AGCR of 22.2%. Specific to neurosurgeons, reimbursement data were available for 52 patients. Charges for neurosurgery providers totaled $290 134 with a total reimbursement of $47 677, yielding an AGCR of 16.4%. For 4 patients, there was no physician reimbursement for any specialty.

Hospital reimbursement data were available for 36 patients, as this data were not accessible for patients admitted before electronic health records (Table 2). Total hospital charges were $3144 392 with a reimbursement of $695 750, yielding an AGCR of 22.1%. Of the 36 patients with both provider and hospital reimbursement data, the total medical charges summed $3556 329, of which $783 834 was reimbursed, producing an AGCR of 22%. Assuming costs were representative over time in our study, extrapolation of these data to all 64 patients estimates grand-total medical charges as $6324 111, with total reimbursement approximating $1393 425.

Illustrative Cases

Patient 1

A 47-yr-old Guatemalan woman was taken into US Border Patrol custody after falling from the border wall. She was brought to (BUMCT), complaining of severe low back pain. On

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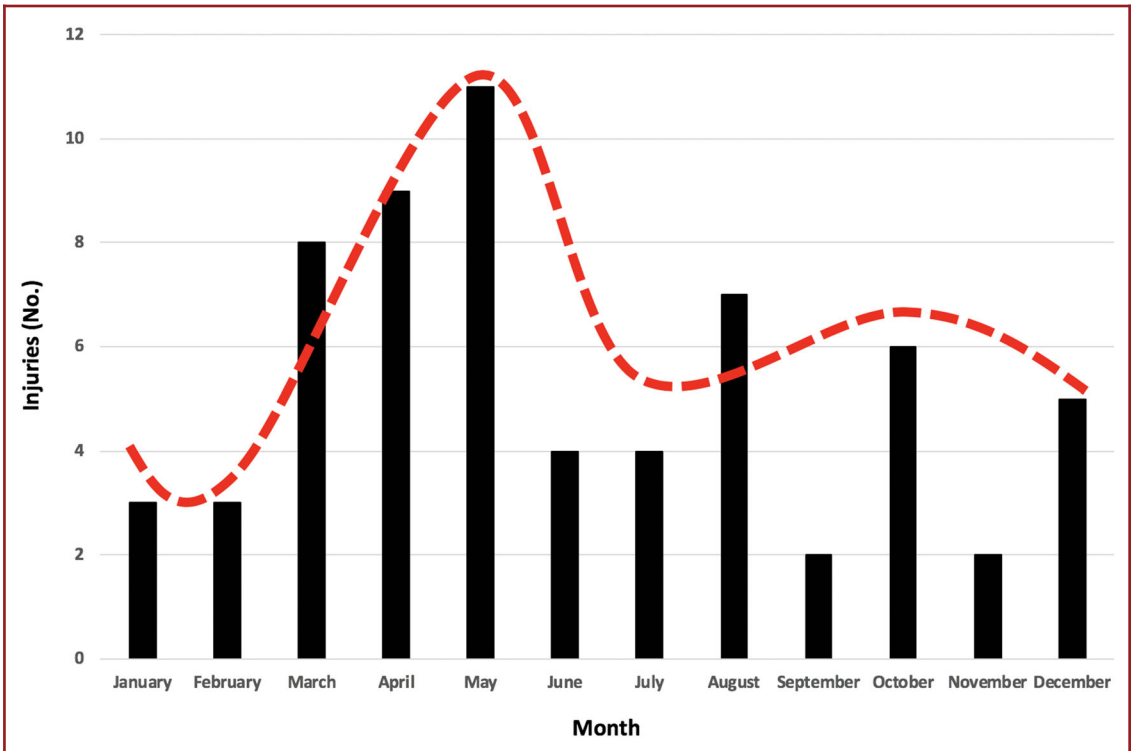


FIGURE 2. *The number of injuries per month throughout the 6-yr study period. Most injuries occurred in the mild months of spring in the absence of the extreme desert heat of summer and below-freezing nocturnal temperatures of winter.*

examination, she was neurologically intact. Computed tomography (CT) imaging revealed an L3 burst fracture with retropulsed bone fragments in the spinal canal. She had no complicating injuries and was taken the following day for decompressive laminectomy and fusion using L2-4 pedicle screws. She remained neurologically intact, and on postoperative day 3, she was deemed safe for discharge "home" (or equivalent).

Case Management and the Guatemalan Consulate determined the patient had attempted entry into the US in order to join her husband in Florida; her 2 young children were in Border Patrol custody. After extensive discussions between Case Management, Border Patrol, and the Guatemalan Consulate, the patient was released on her own recognizance with her children on hospital day 6 under the care of her husband. The patient was lost to follow-up.

Patient 2

This 43-yr-old man sustained a 20-foot fall from the border wall. He was emergently transported to (BUMCT) after complaining of neck pain and inability to move. Neurological examination demonstrated 4/5 strength in both biceps and triceps, 1/5 in both finger flexors, and 0/5 in all other groups distally. Sensation was absent below the C8 dermatome. Rectal tone was absent, making the neurological examination consistent with a C7 ASIA A SCI. Imaging revealed bilateral fracture dislocation with locked facets at C6-7 and a traumatic disc herniation. The patient was taken the same day for a C6/7 anterior cervical discectomy and fusion, in which decompression, realignment, and restoration of cervical lordosis were achieved.

After surgery, the patient's neurological examination remained unimproved. He was reintubated on postoperative day 2 because of respiratory distress and remained in the intensive care unit (ICU), where a tracheostomy was ultimately performed. The patient was transferred directly to an acute care facility in Mexico City on hospital day 14.

Patient 3

A 36-yr-old woman was found alert, oriented, and complaining of severe headache with outward signs of head trauma. Upon arrival in the emergency department she became agitated, confused, and was no longer following commands. CT imaging revealed a right parieto-occipital epidural hematoma. She was intubated for airway protection and taken emergently to the operating room for a right parieto-occipital craniotomy and evacuation of the epidural hematoma.

After surgery, the patient developed severe diabetes insipidus in the ICU. She was extubated on postoperative day 5. Her neurological condition gradually improved but she continued to

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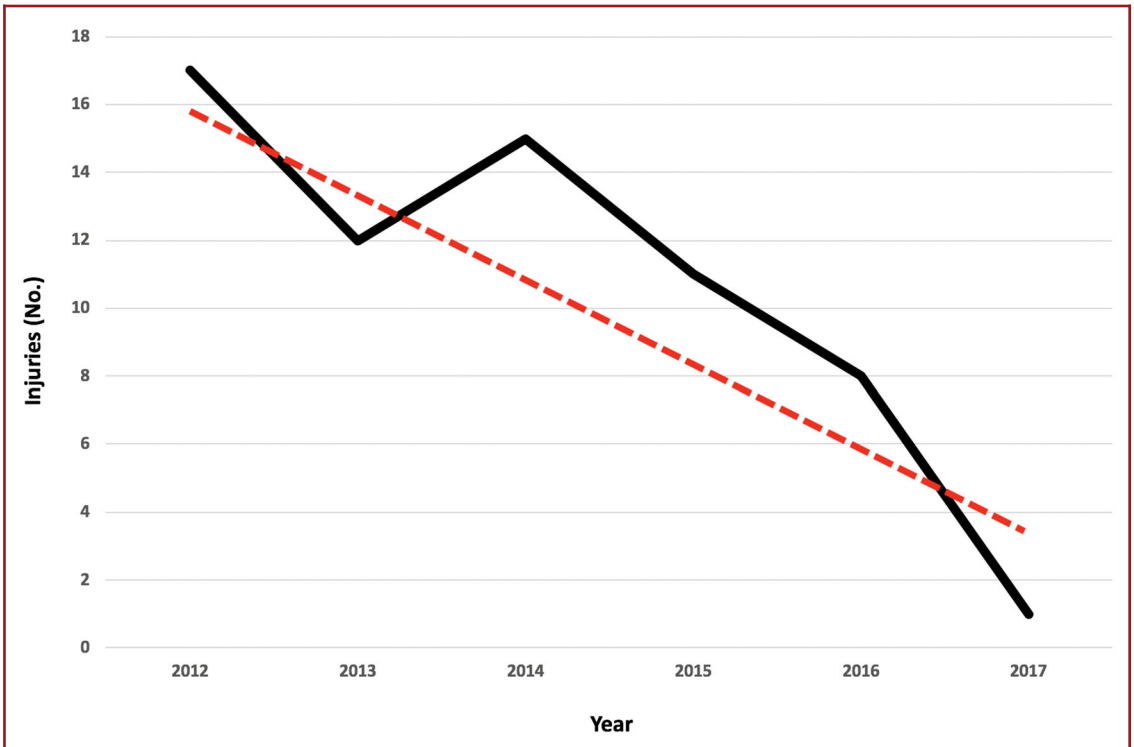


FIGURE 3. *The overall number of neurotrauma injuries statistically significantly trended downward during the study period, which is congruent with decreasing apprehensions by the US Border Patrol since 2010 ($P < .001$).*

TABLE 2. Cost Analysis

	Patients (n)	Total charge	Reimbursement	AGCR (%)
Provider cost				
All providers	60	$672 075	$149 292	22.2
Neurosurgeons	52	$290 134	$47 677	16.4
Hospital cost[a]	36	$3144 392	$695 750	22.1
Total (provider and hospital) cost	36	$3556 329	$783 834	22
Total extrapolated cost[b]	64	$6324 111	$1393 425	22

AGCR, adjusted gross collection rate.
[a]Hospital costs were unattainable for patients admitted before electronic health record.
[b]Total extrapolated cost assumes a static charge of service and reimbursement rate (AGCR) of 22% applied to all 64 patients throughout the study period.

have periods of extreme agitation. Discharge was delayed because of difficulties finding a receiving institution. On day 17, she was transferred to an acute care hospital in Mexico with ongoing confusion and agitation.

DISCUSSION

Cranial and spinal trauma represent a significant proportion of high-acuity injuries in level 1 trauma centers. From estimates of a half million undocumented crossings into the US annually, many of which require scaling a substantial barrier, it is not surprising that the incidence of neurotrauma in the Southern US is significant.[2] In a recent series of orthopedic injuries published at our institution, roughly 40% of all injuries were spine related. Since orthopedic problems comprise the vast majority of these injuries, one can infer spine and cranial injuries together make up almost half of all wall-jumping trauma.[7] Although this constitutes only a portion of incidents from wall-jumping, they represent an extreme and costly end of the traumatic spectrum, and being the only level 1 trauma center in southern Arizona, our institution directly receives almost all of the qualifying trauma from the border wall in the region.

Spine injuries were the most common type of neurotrauma observed in patients jumping over the border wall. Compression and burst fractures are well described after a fall from a height, especially when landing on one's feet.[7-10] In the largest historical series of patients falling from a height of > 1 story, 74% of patients with spine injuries suffered compression or burst

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fractures, similar to the 68% in our population.[8] Scalea et al[10] described 44% of their patients required surgical fixation, which is consistent with the 40% of spine fractures treated with fixation in the current study. Twenty patients required surgical fixation for spine fractures, 5 of whom additionally suffered SCI.

In the US, the average first-year cost following SCI is $523 089 with each subsequent year costing $79 759.[11] The financial burden to care for patients with SCI long term is exceptionally taxing on health care systems. Additionally, the physical and psychological devastation from SCI cannot be overstated, particularly when it occurs in a foreign national attempting to immigrate to another country.

TBI comprised only about 25% of the neurotrauma we observed. This is perhaps due to the propensity of conscious jumpers to land on their feet (in contrast to a true fall). Fortunately, within the current study, most instances of TBI were mild to moderate, with 3 cases of severe TBI requiring intracranial surgery. Nonetheless, TBI was associated with statistically significantly longer LOS relative to spine injury, which is attributable to acute physical and cognitive rehabilitation needs before repatriation to an appropriate facility or discharge into US Border Patrol custody. The total annual cost of TBI within the US is estimated to be over $4.5 billion and represents major socioeconomic implications within trauma.[12] Therefore, even relatively few numbers of TBI in undocumented immigrants carries major socioeconomic repercussions with respect to the health care system in the region.

The overwhelming majority of trauma victims in our series were unable to afford the extensive medical care they required. Across the Southwestern US, publicly allocated dollars become the primary source of funding to provide necessary emergent care. When an undocumented immigrant presents in US Border Patrol custody, it is required at our institution to document the badge number of the agent to qualify for appropriate publicly funded reimbursement of that patient's care, which often may not exceed Medicare reimbursement rates. Within the current socioeconomic and political climate, monetary effects inevitably become the foundation of heated political debate and are of particular relevance.

In reviewing cost data for all neurosurgery cases at (BUMCT) from 2015 to 2017, the average reimbursement was 31%. In the border-jumper population, physician providers were reimbursed 22%. Over approximately 2.5 yr, 36 patients were treated, for which both hospital and provider reimbursement data were available. The grand total of medical charges in this group was $3 556 329, of which $783 834 was reimbursed, yielding an AGCR of roughly 22%. This is considerably below the expected AGCR of approximately 31% for all others with equivalent diagnoses, and it possesses a reimbursement difference of roughly $320 070. If these data are extrapolated to include all 64 patients (since hospital costs are no longer available in our institution for patients admitted before electronic health records), the grand total of medical charges would near $6 324 111, while the total reimbursement would approximate $1 393 425.

A substantial portion of this cost is attributable to the extra time and resources necessary for the appropriate placement of these patients. Many must stay longer than expected so they can be safely discharged to Border Patrol custody. Others have extended stays while case managers and social workers collaborate with international liaisons to appropriately place patients in foreign care facilities, which in conjunction with the complexities of coordinating international transportation, renders discharge placement exceedingly demanding. Additionally, while the extra time for discharge planning lengthens LOS and increases cost, it also renders patients susceptible to numerous iatrogenic and hospital-associated complications.

Unfortunately, it is not uncommon for the US Border Patrol to recover the bodies of immigrants who have either become lost in the desert or stranded by their group, particularly in the hot summer or cold winter months in which desert temperatures are extreme. Not surprisingly, we observed that most injuries occur in the milder months of spring and fall, which allow for a favorable climate in the arduous journey through the southern Arizona desert. This observation is consistent with the increased number of apprehensions by the US Border Patrol seen in these months.[13]

Over a period of 6 yr, there was a decreasing trend in the number of injuries per year from 2012 to 2017, with 17 injuries in 2012 and 1 injury in 2017 (Figure 3). This is congruent with a report released from the Government Accountability Office in 2013 that states illegal crossings have decreased annually, of which the reasons are continually debated as stemming from the wall itself, growing resources provided to the US Border Patrol, and multiple other socioeconomic factors.[14] With increasing political and financial attention given to the area since passing the Secure Fence Act of 2006, it is likely the medical community will continue to encounter fewer such injuries compared to immediately after construction of the border wall. It is also possible that increased funding and resources allocated to the US Border Patrol mean fewer immigrants make it to the point of traversing the fence. In 2010, the Support Our Law Enforcement and Safe Neighborhoods Act Arizona Senate Bill 1070 was enacted, instituting strict anti-immigration standards within Arizona, which may also be contributing to decreasing apprehensions and illegal crossings. However, it cannot be overlooked that jumping over the border wall acts as a deterrent within and of itself, which could at least partially explain the decrease in associated wall-jumping injuries.

Limitations

In almost all cases, patients were discharged or transferred to Mexico in the custody of the US Border Patrol, making follow-up almost impossible and severely limits this study. This study is also limited by its retrospective design. Grand total medical charges and reimbursement, if available in all 64 patients, would have strengthened the cost analysis.

CONCLUSION

Neurotrauma resulting from wall-jumping across the Mexican–US border is a severe and costly injury experienced in many trauma centers within the region. While neurotrauma associated with the border wall is likely to persist as long as the barrier remains in place, our data suggest that the deterrent effect may be real. Health care officials, law enforcement, and politicians must work together on both sides of the border to minimize injury from jumping over the wall as well as reduce economic burden.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors bring to attention the utilization of health care resources due to spinal and/or cranial trauma suffered during attempted crossing of the border wall from the Mexico side. A fairly detailed description of injury types, costs, and management of neurotrauma in this unique setting allows the reader to better appreciate the impact of wall-jumping on US trauma centers in the vicinity of the border wall. In addition to the human cost associated with injury sustained from wall jumping, the delivery of health care is complicated by the lower rates for reimbursement, which imposes an economic cost on the health care system. However, based on the data presented here, there is reason to be optimistic on account of steady decline in neurotrauma attributed to attempted border crossing over the years. Taken together, the paper presents data on a unique subset of patient population, which should serve as a valuable addition to the sparse literature on the topic.

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Unauthorized entry at the United States-Mexico border is a highly charged topic in the current political landscape. Injury from border wall crossing is an often-overlooked consequence of this phenomenon. Authors from a level-1 trauma center near the Arizona-Mexico border present their neurosurgical experience with this unique patient population. The vast majority of neurosurgical injuries were thoracolumbar compression and/or burst fractures, which is not surprising given the expected high axial load from wall jumping. Traumatic brain injury represented approximately 25% of the observed neurotrauma. A basic cost and reimbursement analysis was provided and suggests that these injuries are costly to our health care system. Interestingly, brain and spine injuries from this mechanism have been on a steady decline year after year, which correlates well with government-issued data demonstrating a decline in border wall crossing during the same time period. This article highlights a potentially under-emphasized topic surrounding border security and is a valuable contribution to our literature.

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The corresponding abstract for this article was presented on Wednesday, September 19, 2018 at the Eurospine 2018 Conference in Barcelona, Spain.

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Received, April 2, 2018.
Accepted, January 29, 2019.
Published Online, March 8, 2019.

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Indicators for Nonroutine Discharge Following Cervical Deformity-Corrective Surgery: Radiographic, Surgical, and Patient-Related Factors

BACKGROUND: Nonroutine discharge, including discharge to inpatient rehab and skilled nursing facilities, is associated with increased cost-of-care. Given the rising prevalence of cervical deformity (CD)-corrective surgery and the necessity of value-based healthcare, it is important to identify indicators for nonroutine discharge.

OBJECTIVE: To identify factors associated with nonroutine discharge after CD-corrective surgery using a statistical learning algorithm.

METHODS: A retrospective review of patients ≥18 yr with discharge and baseline (BL) radiographic data. Conditional inference decision trees identified factors associated with nonroutine discharge and cut-off points at which factors were significantly associated with discharge status. A conditional variable importance table used nonreplacement sampling set of 10 000 conditional inference trees to identify influential patient/surgical factors. The binary logistic regression indicated odds of nonroutine discharge for patients with influential factors at significant cut-off points.

RESULTS: Of 138 patients (61 yr, 63% female) undergoing surgery for CD (8 ± 5 levels; 49% posterior approach, 16% anterior, and 35% combined), 29% experienced nonroutine discharge. BL cervical/upper-cervical malalignment showed the strongest relationship with nonroutine discharge: C1 slope ≥ 14°, C2 slope ≥ 57°, TS-CL ≥ 57°. Patient-related factors associated with nonroutine discharge included BL gait impairment, age ≥ 59 yr and apex of CD primary driver ≥ C7. The only surgical factor associated with nonroutine discharge was fusion ≥ 8 levels. There was no relationship between nonhome discharge and reoperation within 6 mo or 1 yr (both $P > .05$) of index procedure. Despite no differences in BL EQ-5D ($P = .946$), nonroutine discharge patients had inferior 1-yr postoperative EQ-5D scores ($P = .044$).

CONCLUSION: Severe preoperative cervical malalignment was strongly associated with nonroutine discharge following CD-corrective surgery. Age, deformity driver, and ≥ 8 level fusions were also associated with nonroutine discharge and should be taken into account to improve patient counseling and health care resource allocation.

KEY WORDS: Cervical deformity, Surgery, Discharge, CD, Rehabilitation, Skilled nursing facility, Outcomes

Neurosurgery 85:E509–E519, 2019 DOI:10.1093/neuros/nyz016 www.neurosurgery-online.com

Outcomes following cervical deformity (CD)-corrective surgery are a subject of increased attention in the literature, with recent reports aiming to identify treatment strategies associated with satisfactory postoperative clinical gains.[1] Although numerous reports show favorable clinical outcomes following CD-corrective surgery, the postoperative course of

ABBREVIATIONS: BL, baseline; **BMI,** body mass index; **CCI,** Charlson Comorbidity Index; **CD,** cervical deformity; **CI,** confidence interval; **CL,** cervical lordosis; **cSVA,** cervical sagittal vertical axis; **EBL,** estimated blood loss; **HRQL,** health-related quality-of-life; **ISSG,** International Spine Study Group; **LL,** lumbar lordosis; **LOS,** length of stay; **mJOA,** Modified Japanese Orthopaedic Association questionnaire; **NDI,** Neck Disability Index; **OR,** odds ratios; **PI,** pelvic incidence; **QOL,** Quality-of- Life; **TK,** thoracic kyphosis

recovery may be protracted and expensive, with total surgical costs-of-care surpassing $55 000.[2–4] Given the high physical and financial burdens of CD-corrective surgery, it is important to identify surgical and patient-related factors that both contribute to satisfactory clinical outcomes and reduce the overall cost associated with CD-corrective surgery.

A key factor associated with both increased cost-of-care and increased readmission rate following spine surgery is nonroutine discharge, including delayed discharge, discharge to inpatient rehab, and discharge to skilled nursing facilities.[5] Previous research shows a significant relationship between discharge status and increased hospital charges, with 1 study showing a $15 000 cost difference between routine and nonroutine discharge.[6] Discharge to subacute care and inpatient rehab also places patients at increased risk for hospital-acquired conditions like infection, further highlighting the need to limit rates of nonhome discharge.[7] As such, identifying factors associated with nonroutine discharge is critical for reducing hospital costs and improving patient outcomes.

Indicators of nonroutine discharge have previously been investigated for patients undergoing anterior cervical discectomy and fusion, as well as patients undergoing lumbar spine surgery.[8,9] That said, there is a paucity in the literature of studies investigating indicators for nonroutine discharge following CD-corrective surgery. As such, the goal of this study is to use a statistical learning algorithm to identify complications, surgical variables, and patient-related factors associated with nonroutine discharge following CD-corrective surgery.

METHODS

Data Source

This analysis is a retrospective review of a prospective, multicenter database of patients with surgical CD enrolled from 2013 to 2017 at 13 spine surgery centers across the United States. Patients included in the database were ≥18 yr and presented radiographic evidence of CD, defined by the presence of at least 1 of the following on BL imaging: cervical kyphosis (C2-7 Cobb angle >10°), cervical scoliosis (C2-7 coronal Cobb angle <10°), and C2-7 sagittal vertical axis (cSVA) >40 mm or chin-brow vertical angle (CBVA) >25°. All participating centers obtained the institutional review board approval prior to patient enrollment, and all participating patients provided consent prior to enrollment. Additional inclusion criteria for the present analysis included available discharge status data.

Data Collection and Radiographic Assessment

Demographic and clinical data were collected from patients at the preoperative interval and included age, sex, body mass index (BMI), comorbidity status, and Charlson Comorbidity Index (CCI). Operative and complication data were collected following surgery, including operative time, estimated blood loss (EBL), surgical approach, instrumentation used, osteotomy utilization, number of levels fused, complications, reoperations, duration of stay in intensive care, hospital length of stay (LOS), and discharge status, including discharge to home, inpatient rehab, or skilled nursing facility. Health-related quality-of-life (HRQL) scores, including outcomes of the EuroQol-5D-3 L (EQ-5D), Quality-of-Life (QOL) in swallowing disorders, and Neck Disability Index (NDI) questionnaires, were collected at BL and at the 1-yr postoperative interval. Modified Japanese Orthopaedic Association questionnaire (mJOA) score was collected at BL and at the 3-mo postoperative interval to assess myelopathy severity.

Preoperative radiographs were collected from neutral cervical anterior-posterior and lateral images, and were analyzed with SpineView® (ENSAM, Laboratory of Biomechanics, Paris, France) software according to previously published techniques.[10–12] Cervical and upper-cervical radiographic parameters were assessed as previously published and included cervical lordosis (CL), cervical sagittal vertical axis (cSVA), C2-T3 CL, cSVA from C2-T3, C2 slope, C1 slope, C0 slope, T1 slope, T1 slope minus CL (TS-CL), McGregor's slope (McGS), and upper cervical curvature (C0-C2 angle).[13]

Global and spinopelvic parameters were also assessed as previously published and included lumbar lordosis (LL), thoracic kyphosis (TK), C7-S1 SVA, pelvic tilt, pelvic incidence (PI), mismatch between PI and LL (PI-LL), and C2-S1 angle.[13]

Statistical Analysis

Patients were stratified into groups by discharge type: home or nonroutine (discharge to inpatient rehab or skilled nursing facility). Overall demographic, surgical, and clinical data were first summarized with descriptive statistics, and then compared between discharge groups by using chi-squared and independent samples *t*-tests, as appropriate. Primary analysis was conducted by using the R statistical software package (version 3.2.4, R Foundation for Statistical Computing, Vienna, Austria), and it identified factors associated with nonroutine discharge. A nonreplacement sampling set of 10 000 conditional inference trees identified potential factors influential of nonroutine discharge as well as the respective importance of each variable as an indicator of nonroutine discharge. Specifically, from a pool of 267 available demographic, clinical, surgical, and radiographic variables, the top indicators of nonroutine discharge were selected according to a variable importance table, which was generated as per the conditional permutation importance defined by the "varimp" function within the R "party" package.[14] An additional conditional inference tree analysis assessed significant cut-off points at which these variables were associated with nonroutine discharge status.

Secondary analysis further confirmed associations between discharge status and radiographic, patient, and surgical factors with binary logistic regression, reporting the odds ratio (OR, [95% confidence interval (CI)]) of nonroutine discharge for continuous variables and for dichotomized variables at their respective significant cut-offs. Finally, by using the

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TABLE 1. Overall Demographic, Comorbidity, and Surgical Description of the Entire Patient Cohort

Demographic description	
Age (yr)	61.3 ± 10.5
Sex (% female)	63.0%
BMI (kg/m^2)	29.4 ± 7.9
CCI	0.90 ± 1.24
History of smoking	33.1%
Diabetes mellitus	8.1%
Osteoporosis	14.8%
Depression	31.9%
Surgical description	
Levels fused	8.2 ± 4.6
EBL (cc's)	845.0 ± 878.7
Operative time (min)	488.7 ± 314.4
Approach	
Anterior	15.9%
Posterior	49.3%
Combined	34.9%
Osteotomy	
Any	55.8%
Smith-Petersen	23.2%
Pedicle subtraction	14.5%
Vertebral column resection	4.3%
Decompression	56.5%

factors identified as associated with nonroutine discharge from the variable importance table as independent variables, forward stepwise multivariable linear regression was used to assess combinations of preoperative factors most strongly associated with nonroutine discharge status, controlling for fusion length and demographic variables that differed between discharge groups in univariate analysis. Descriptive analysis, secondary analysis, and all means comparison tests were performed by using SPSS software (v21.0, IBM, Armonk, New York).

RESULTS

Study Participants and Patient Characteristics

Overall, 138 surgical CD patients were included in the present analysis. Breakdown of patient discharge location was 71% home and 29% nonroutine (including 21% to inpatient rehab and 8% to skilled nursing facilities). Table 1 presents a demographic and surgical summary of the overall patient population. At BL, the overall cohort showed moderate-to-severe cervical malalignment, with a mean TS-CL of 38.0° ± 18.1° and a mean cSVA of 46.7 mm ± 24.9 mm. Table 2 presents univariate differences between patient cohorts with respect to patient and surgical factors.

Patient-Related and Procedural Indicators of Discharge Outcome

BL patient demographics and functional status were associated with nonroutine discharge (Table 3). Specifically, in descending order of strongest association, BL physician-reported gait impairment (OR: 5.29; 95% CI: [2.25-12.42]), communication impairment as assessed by QOL in Swallowing Disorders questionnaire communication score ≤52 (OR: 4.22; 95% CI: [1.55-11.50]), and age ≥59 yr (OR: 4.25; 95% CI: [1.63-11.05]) were all indicative of nonroutine discharge. The only procedural factor associated with nonroutine discharge status was fusion ≥8 levels (OR: 4.03; 95% CI: [1.78-8.56]). As continuous variables, age (Figure 1; OR: 1.08; 95% CI: [1.03-1.23]) and fusion length (OR: 1.16; 95% CI: [1.06-1.27]) were still associated with nonroutine discharge, although with lower odds than their respective dichotomized counterparts.

Radiographic Indicators of Discharge Outcome

Upper-cervical malalignment was also associated with nonroutine discharge, with C1 slope ≥14° (OR: 8.35, [3.07-22.71]) and C2 slope ≥57° (OR: 6.95, [1.79-8.91]) showing the strongest relationships with discharge status out of all radiographic parameters assessed (Table 3). Although the associations of cervical parameters were smaller than those of upper-cervical parameters, TS-CL ≥57° (OR: 5.89, [2.19-15.85]) and cSVA ≥ 40 mm (OR: 4.63, [1.97-10.87]), were still indicative of nonroutine discharge. The only noncervical radiographic parameters associated with nonroutine discharge were TK ≤−57° (OR: 3.85, [1.78-8.35]) and C2-S1 angle ≤−22° (OR: 4.75, [1.92-11.74]). Structural driver of deformity was also identified as an indicator of discharge status, as patients with primary CD drivers below C7 showed a significantly increased probability of nonroutine discharge (OR: 3.90, [1.78-8.56]). Assessed as continuous variables, all radiographic parameters described in the above analysis, including C1 slope (Figure 2), were significantly associated with nonroutine discharge, although the odds of nonroutine discharge were lower when treating these variables as continuous rather than dichotomous indicators (Table 4).

Complication Indicators of Discharge Outcome

The overall complication rate was significantly higher for nonroutine discharge patients (home: 59.2% vs nonroutine: 77.5%, $P = .041$). Development of multiple complications (OR: 4.16, [1.87-9.22]) and hospital LOS ≥ 6 d were associated with nonroutine discharge (Table 3), as were EBL ≥ 900cc (OR: 3.56, [1.65-7.67]), admission to surgical intensive care unit (OR: 5.35, [1.93-14.82]), and neurologic adverse events (OR: 2.76, [1.19-6.41]). When treated as continuous variables, number of complications (Figure 3; OR: 1.5 [1.18-1.98]) and LOS (OR: 1.17 [1.04-1.30]) were associated with increased odds of nonroutine discharge; EBL was not (OR: 1.0 [1.000-1.001]). There was no relationship between nonroutine discharge and reoperation within 3 mo ($P = .249$), 6 mo ($P = .793$), or 1 yr ($P = .814$) of index procedure.

Multivariable Regression Modeling of Discharge Indicators

Controlling for fusion length and age, the following combination of preoperative patient-related and radiographic factors were responsible for 27.3% of the variation in discharge status

TABLE 2. Univariate Comparison of Demographic and Surgical Factors Between Home Discharge and Nonroutine Discharge Patient Groups

	Home discharge	Nonroutine discharge	*P*-value
Demographic comparison			
Age (yr)	59.3 ± 10.5	66.4 ± 8.5	<.001
Sex (% female)	62.5%	64.1%	.861
BMI (kg/m^2)	28.8 ± 7.5	31.0 ± 8.8	.162
CCI	0.91 ± 1.22	0.88 ± 1.32	.916
Surgical comparison			
Levels fused	7.3 ± 4.2	10.3 ± 4.8	<.001
EBL (cc's)	749 ± 841	1081 ± 934	.044
Operative time (min)	476 ± 271	519 ± 403	.477
Approach			
Anterior	20.4%	5.0%	.025
Posterior	46.9%	55.0%	.390
Combined	32.7%	40.0%	.411
Osteotomy			
Any	52.0%	65.0%	.164
Smith-Petersen	24.5%	20.0%	.571
Pedicle subtraction	10.2%	25.0%	.025
Vertebral column resection	1.0%%	12.5%	.003
Decompression	50.0%	72.5%	.016

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($R^2 = 0.273$, $P < .001$): gait impairment ($\beta = 0.081$), C0 Slope ($\beta = 0.015$), and McGregor's Slope ($\beta = 0.016$).

Myelopathy Outcomes by Discharge Group

At BL and 3-mo intervals, 89.9% and 77.5% of patients had available mJOA information. Nonroutine discharge patients presented with more severe myelopathy, as assessed by mJOA score (home: 14.0 ± 2.8 vs nonroutine: 12.8 ± 2.4, $P = .037$). Assessed by specific subsection of the mJOA questionnaire, nonroutine discharge patients presented with more severe myelopathic motor dysfunction in the lower extremities (home: 5.0 ± 1.4 vs nonroutine: 3.9 ± 1.1, $P < .001$). The groups did not differ in BL myelopathic dysfunction of the upper extremities ($P = .238$), sensory loss ($P = .783$) or sphincter dysfunction ($P = .805$). At 3-mo postoperative, nonroutine discharge patients continued to show inferior overall mJOA (home: 14.7 ± 2.5 vs nonroutine: 12.7 ± 2.9, $P = .001$), and myelopathic lower-extremity (home: 5.3 ± 1.6 vs nonroutine: 4.0 ± 1.7, $P < .001$) scores. Patient groups did not differ in 3-mo upper-extremity ($P = .057$), sensory loss ($P = .783$), or sphincter ($P = .084$) scores.

Patient-Reported Outcomes by Discharge Group

Overall, 95 (68.8%) of included patients had available 1-yr postoperative HRQL follow-up, with no difference between discharge groups in rates of 1-yr HRQL follow-up (home: 68.3%, nonroutine: 70.0%, $P = .851$). Nonroutine discharge patients showed inferior EQ-5D outcomes at 1-yr postoperative follow-up (home: 0.79 ± 0.07 vs nonroutine: 0.76 ± 0.08, $P = .034$), despite no significant difference in BL EQ-5D scores between discharge groups (home: 0.73 ± 0.07 vs nonroutine: 0.73 ± 0.06, $P = .946$). There were no significant differences in NDI scores between patient groups at BL (50.2 ± 18.5 vs 46.2 ± 16.4, $P = .237$) or 1-yr (35.6 ± 20.6 vs 40.0 ± 20.6, $P = .337$) follow-up.

Case Example

Preoperative and postoperative lateral radiographs of a patient discharged home and a patient discharged to a skilled nursing facility (Figure 4A and 4B, respectively). Preoperatively, the patient in Figure 4B presented with a number of factors associated with increased odds of nonroutine discharge, including age <59 yr (home: 50 yr vs nonroutine: 61 yr), and more severe upper-cervical malalignment (C2 Slope, home: 19° vs nonroutine: 71°), TS-CL (Home: 25° vs Nonroutine: 74°), and cSVA (home: 17 mm vs nonroutine: 45 mm). The nonroutine discharge patient also underwent a longer fusion (home: 7 levels vs nonroutine: 8 levels) that met the threshold associated with increased odds of nonroutine discharge (≥8 levels) identified in this study.

DISCUSSION

Cervical spine surgery is increasingly common in the United States, with multiple studies showing a marked increase in the rate of surgery for degenerative cervical pathologies over the past few decades.[15,16] Despite advancements in surgical technique and the standardized classification of CD, CD-corrective surgery remains challenging due to the disease's complex etiology and a typically heterogeneous patient population.[1,17] While clinical outcomes following CD-corrective surgery are generally favorable, small-scale studies report postoperative nonroutine discharge rates as

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TABLE 3. Top Patient-Related, Procedural, Complication, and Radiographic Factors Associated With Nonroutine Discharge Following Corrective Surgery for CD

Overall rank	Factor associated with nonroutine discharge	Groups compared: 1 (*N*) vs 2 (*N*)	Proportion of discharge to nonroutine		*P*-value	OR	95% Confidence interval	
			Group 1	Group 2			Lower	Upper
BL patient-related predictors								
2	Gait impairment	Yes (31) vs no (106)	58.1%	20.8%	$P < .001$	5.29	2.25	12.42
7	SWAL communication ≤52	≤52 (19) vs ≥53 (118)	57.9%	24.6%	$P = .005$	4.22	1.55	11.50
8	Age ≥ 59 yr	≤58 yr (90) vs ≥59 yr (48)	12.5%	37.8%	$P = .003$	4.25	1.63	11.05
Procedural predictors								
12	Levels fused ≥8	≤7 (61) vs ≥8 (69)	17.3%	45.9%	$P = .001$	4.03	1.81	8.98
Complication predictors								
5	Number of complications ≥ 2	≤1 (39) vs ≥2 (99)	20.2%	51.2%	$P < .001$	4.16	1.87	9.22
6	Postoperative LOS ≥ 6 d	≤5 d (68) vs ≥6 d (70)	15.7%	42.7%	$P < .001$	3.99	1.79	8.91
9	EBL ≥ 900 cc	≤899 (88) vs ≥900 cc (50)	19.3%	46.0%	$P = .001$	3.56	1.65	7.67
13	Stay in surgical ICU	Yes (90) vs no (47)	38.9%	10.6%	$P = .001$	5.35	1.93	14.82
16	Any neurologic complication	Yes (30) vs no (108)	46.7%	24.0%	$P = .018$	2.76	1.19	6.41
BL radiographic predictors								
1	C1 Slope ≥ 14°	<14° (107) vs ≥14° (23)	21.5%	69.6%	$P < .001$	8.35	3.07	22.71
3	C2 Slope ≥ 57°	<57° (113) vs ≥57° (23)	21.2%	65.2%	$P < .001$	6.95	2.64	18.33
4	TS-CL ≥ 57°	<57° (111) vs ≥57° (21)	21.6%	61.9%	$P < .001$	5.89	2.19	15.85
10	Apex of primary driver ≥ C7	≤C6 (75) vs ≥C7 (60)	17.3%	45.0%	$P = .001$	3.90	1.78	8.56
11	C2-S1≤ −22°	≤−22° (27) vs > -22° (96)	55.6%	20.8%	$P = .001$	4.75	1.92	11.74
14	C0 Slope ≥ −0.66°	<-0.66 (80) vs ≥-0.66° (47)	18.7%	48.9%	$P < .001$	4.15	1.86	9.26
15	cSVA ≥ 40 mm	<40 mm (67) vs ≥40 mm (67)	13.4%	41.8%	$P < .001$	4.63	1.97	10.87
17	T2-T12 Kyphosis ≤ −51°	≤−51° (54) vs >−51° (82)	46.3%	18.3%	$P = .001$	3.85	1.78	8.35
18	McGregor's Slope ≥ 1.9°	<1.9° (58) vs ≥1.9° (56)	15.5%	42.7%	$P = .002$	4.08	1.68	9.91

OR from binary logistic regression indicate odds of nonroutine discharge for each factor at the factor's respective cut-off point. ICU = intensive care unit.

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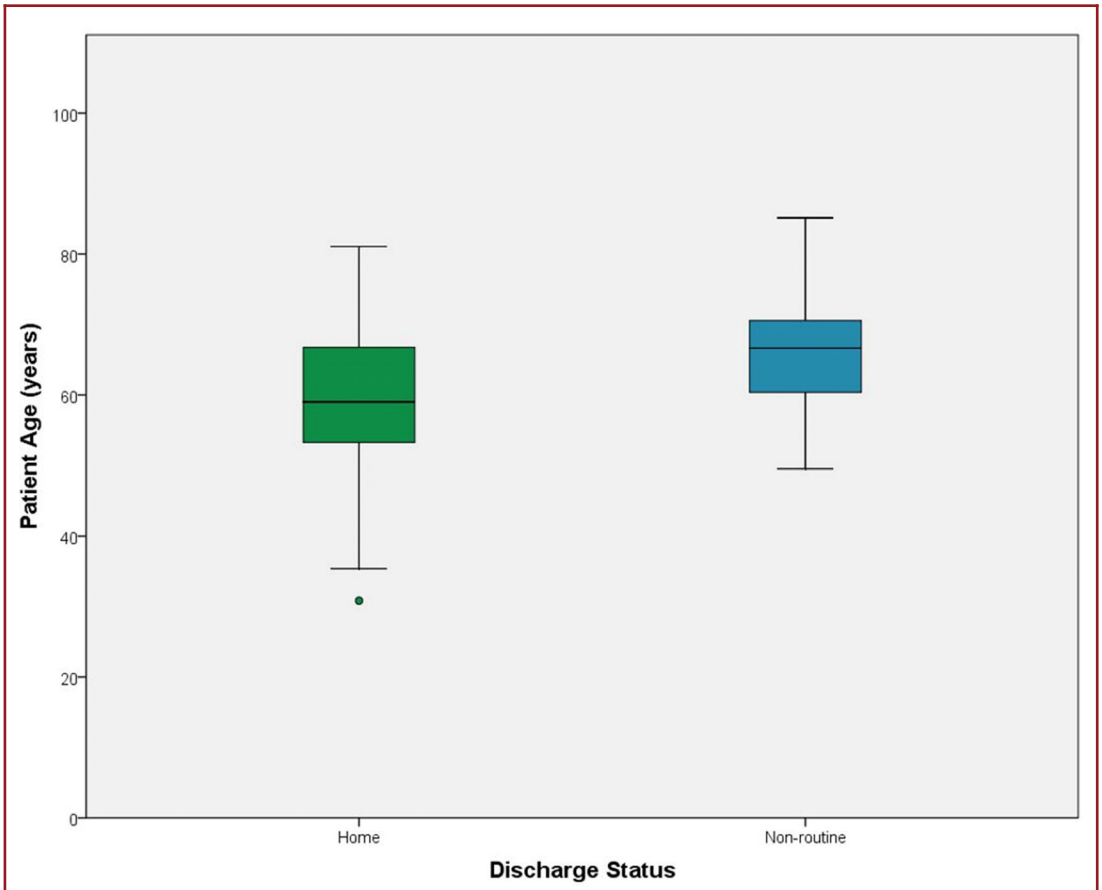


FIGURE 1. *Boxplot displaying the age distributions for patients with nonroutine discharge status and patients discharged home. Points represent outliers that do not fall within the inner fences.*

high as 40%.[18] Nonroutine discharge, including discharge to subacute care and inpatient rehab, has previously been associated with increased cost-of-care following spine surgery, and may place patients at higher risk for hospital-acquired conditions like nosocomial infection.[7,19] The present study aimed to identify independent factors associated with nonroutine discharge, as such indicators can be used to improve preoperative patient counseling and risk stratification.

Key Results

Factors associated with nonroutine discharge following CD-corrective surgery are undercharacterized in the literature, primarily due to the fact that CD has only recently been classified as a distinct clinical entity.[17] Our study identified multiple surgical and patient-related variables associated with nonroutine discharge following CD-corrective surgery, the strongest of which were preoperative cervical and upper-cervical malalignment. Controlling for the covariates of age and fusion length, multivariable regression analysis further showed upper-cervical malalignment (as assessed by C0 Slope and McGregor's Slope) as being associated with nonroutine discharge. Assessing the relationship between the radiographic alignment and discharge destination is particularly novel, as similar investigations in the literature base their analyses on large nationwide databases lacking in radiographic granularity.[20,21] Additionally, investigating cervical sagittal alignment as associated with nonroutine discharge is especially important in the context of CD, as severe preoperative cervical and upper-cervical sagittal malalignment have previously been correlated with inferior outcomes following surgical CD correction.[4,22] In suggesting a relationship between severe cervical malalignment and discharge destination, our results allow for better-informed preoperative counseling for high-risk patients regarding their care after surgery.

Interpretation

While our study identified statistically meaningful cut-offs at which various radiographic parameters were associated with nonroutine discharge, this does not necessarily mean that the cutoffs should be interpreted as strict indicators. Statistical

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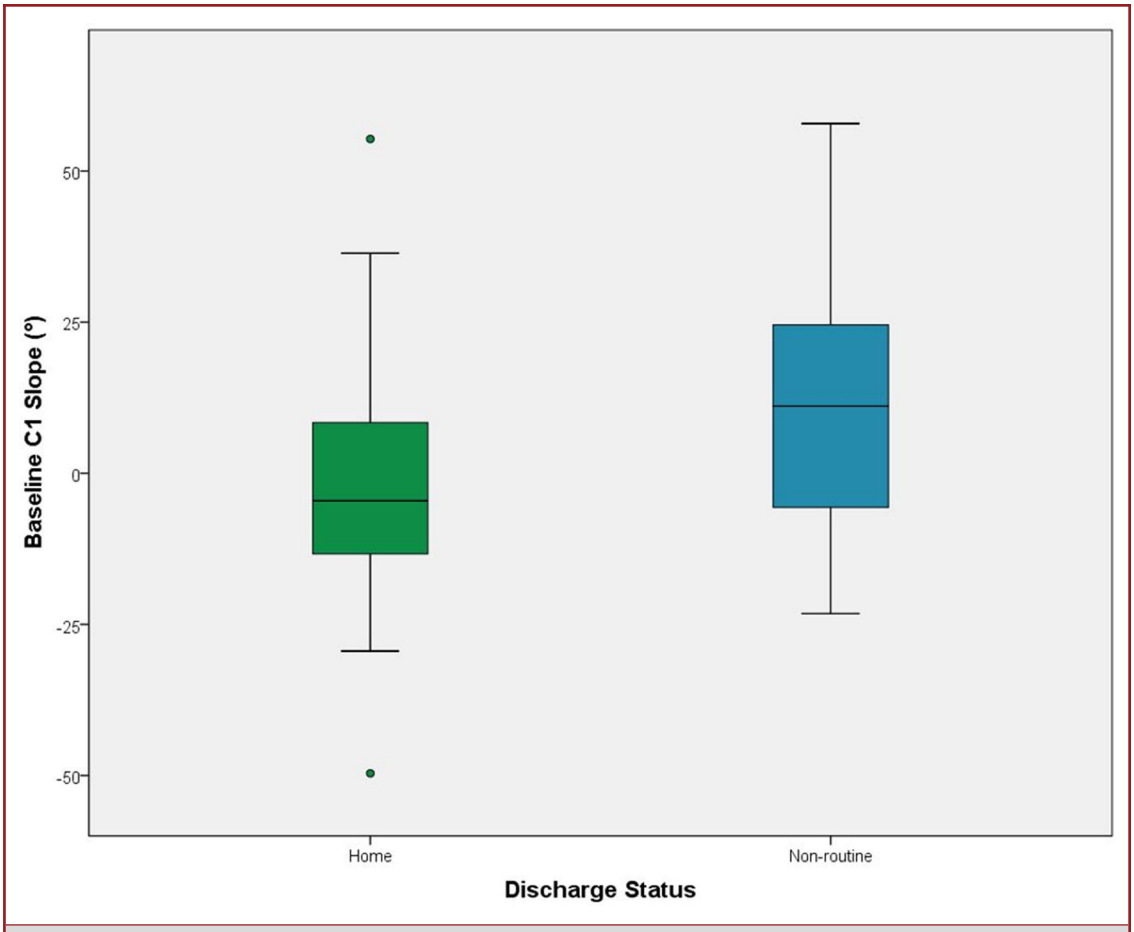


FIGURE 2. *Boxplot displaying the C1 slope distributions for patients with nonroutine discharge status and patients discharged home. Points represent outliers that do not fall within the inner fences.*

significance does not always equate to clinical relevance; for example, a patient with a cSVA of 39 mm does not necessarily have substantially lower odds of nonroutine discharge as compared to a similar patient with a cSVA of 4 mm. Indeed, when assessed as continuous variables, the radiographic factors assessed in this study were still associated with discharge destination, demonstrating a trend of increasing odds of nonroutine discharge with increasing severity of radiographic deformity. Furthermore, given previous research showing strong correlations between upper-cervical and subaxial radiographic alignment, it is possible that some of these radiographic predictors are acting as moderator variables for other independent predictors of discharge.[23] In light of this, we suggest that the radiographic indicators and respective cutoffs identified in our study should be interpreted as tools for use in the greater context of spinopelvic alignment to predict nonroutine discharge after CD-corrective surgery.

It is important to note that when using OR as a measure of association with discharge status, one must take into account the proportion of patients experiencing nonroutine discharge. The risk of nonroutine discharge and the odds of nonroutine discharge are not necessarily interchangeable. Specifically, as the probability of nonroutine discharge increases, the odds and risk ratio diverge, with the corresponding OR growing larger than the corresponding risk ratio.[24] The upshot is a more extreme OR, which should be taken into account when interpreting the results of factors like gait impairment, which in our analysis had an OR of 5.29 but a relative risk ratio of 1.94 (95% CI: 1.15-3.26). Still, this analysis is a logistic regression-based case-control study in which patients were grouped by their outcomes, not their exposures. As such, the use of OR as a measure of association is justified as absolute risk, and therefore relative risk cannot be calculated accurately.[25,26]

Previous literature on discharge destination following spine surgery has primarily focused on patients undergoing lumbar decompression or fusion.[8,21] One of the few studies investigating indicators of discharge location following cervical surgery also showed patient age, preoperative functional status, and operative

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TABLE 4. Top Radiographic Factors Associated With Nonroutine Discharge Following Corrective Surgery for CD

Continuous indicator of nonroutine discharge	*P*-value	OR	95% Confidence interval	
			Lower	Upper
C1 Slope	$P < .001$	1.05	1.02	1.07
C2 Slope	$P = .003$	1.03	1.01	1.05
TS-CL	$P = .008$	1.03	1.01	1.06
C2-S1	$P = .017$	0.98	0.961	0.996
C0 Slope	$P = .001$	1.05	1.02	1.08
cSVA	$P = .006$	1.03	1.01	1.05
T2-T12 Kyphosis	$P = .024$	0.98	0.961	0.997
McGregor's Slope	$P = .008$	1.04	1.01	1.07

OR from binary logistic regression indicate associated odds of nonroutine discharge for each continuous radiographic parameter.

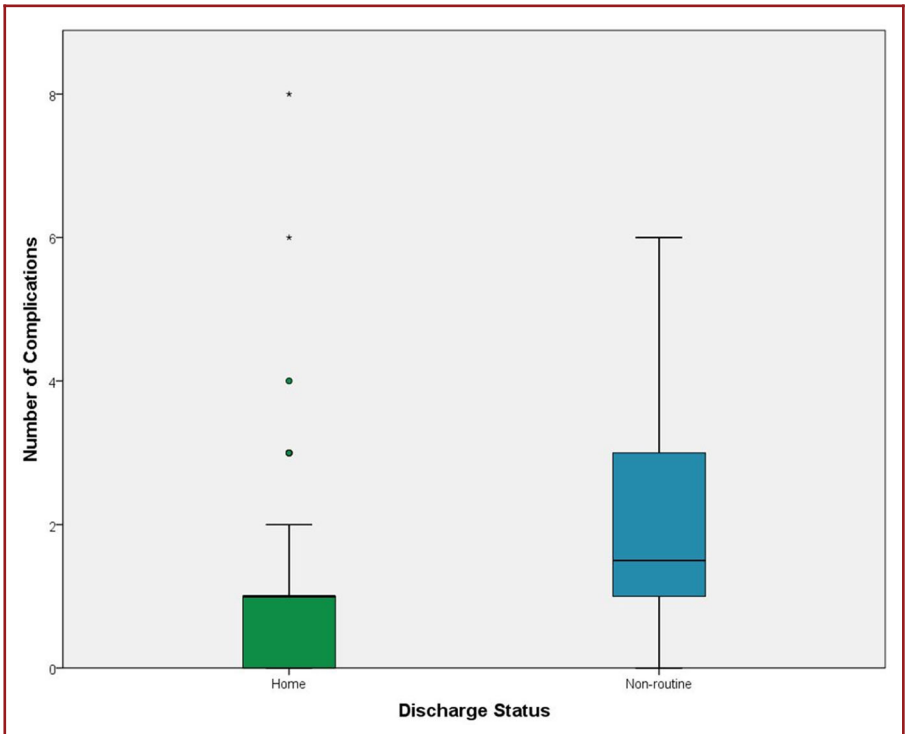


FIGURE 3. *Boxplot displaying the complication number distributions for patients with nonroutine discharge status and patients discharged home. Points represent outliers that do not fall within the inner fences; asterisks represent extreme outliers with values more than 3 times the height of the boxes.*

time as associated with patient discharge to a facility other than home.[9] Our results substantiate these reports, similarly demonstrating age ≥59 yr, ≥8 level fusion, and multiple complications as indicative of nonhome discharge. As the literature also suggests a strong correlation between age and frailty, future research should investigate frailty as an indicator of nonroutine discharge in operative CD patients.[27]

In addition to the factors mentioned above, our results show an increased risk of nonroutine discharge for patients with primary structural drivers of CD below C7. These results were based upon a recent investigation of 73 CD patients, which similarly showed inferior postoperative outcomes for patients with CD drivers in the thoracic spine.[28] Specifically, patients with thoracic drivers of deformity showed no improvement in HRQL at the 1-yr postoperative interval and were significantly more likely to have persistent severe TS-CL deformity. While cervical sagittal alignment is certainly an important consideration in the preoperative assessment of CD, the interdependence of the cervical,

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FIGURE 4. *Case example: preoperative (left) and postoperative (right) cervical lateral radiographs for* **A**, *a patient discharged home following surgery and* **B**, *a patient discharged to a skilled nursing facility. Patient A presented with considerably less severe deformity, as assessed by C2 slope (Patient A: 19° vs Patient B: 71°), TS-CL (Patient A: 25° vs Patient B: 74°), and cSVA (Patient A: 17 mm vs Patient B: 45 mm). Patient A was also younger (Patient A: 50 yr vs Patient B: 61 yr) and underwent a shorter fusion (Patient A: 7 levels vs Patient B: 8 levels).*

thoracolumbar, and lumbopelvic curves in the context of CD is gaining increased attention in the literature.[29,30] The results of the present study further emphasize the importance of the full spine, not just the cervical region, in influencing outcomes following CD-corrective surgery.

Although discharge to subacute care may be a necessary part of the recovery process for patients undergoing complex CD-corrective surgery, efficient allocation of health care resources necessitates effective preoperative risk stratification. Indeed, while the nationwide average for hospital LOS has decreased over the past few decades, discharges to postacute care facilities have increased by nearly 50%.[31] In helping identify patients with increased odds of nonroutine discharge, the present study serves as a jumping-off point for preoperative patient–surgeon discussions about discharge status and expectations for recovery. Hopefully, this will allow patients, patient families, insurance providers, and postacute care facilities to better plan for the likelihood of requiring additional health care services after surgery.

Limitations

An important limitation of this analysis was our inability to account for social and patient-related factors, such as family support system, social history, and insurance status, which could all potentially affect the discharge destination. Decisions

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regarding patient discharge destination following surgery are multi-disciplinary, often taking into account guidance from physical and occupational therapists, as well as social factors like caregiver status and community support. As these variables were not included in the database, we were unable to adequately control for these potentially significant confounders. Given this limitation, it is important to emphasize that our findings present factors correlated with nonroutine discharge; they do not speak to causative factors.

Additionally, small sample size reduces the statistical power of our findings and raises the possibility of spurious predictors due to statistical noise. The small sample size is reflected in the relatively wide confidence intervals of our regression analyses. Our results likely reflect a spectrum of variables associated with discharge status: those actually associated with nonroutine discharge, those serving as moderator variables for other factors, and those incorrectly identified as being associated with nonroutine discharge because of small sample size. Future large-scale studies with more statistical power to control for bias are needed to further confirm the findings of this study. Lastly, the present analysis lacks external validity, and thus the generalizability of our conclusions to a broader CD patient population is uncertain. Our results reflect experienced deformity surgeons with specific practice patterns treating patients at tertiary spine centers, and as such, the results may not be applicable to all spinal surgeons in all settings. Despite this, the multicenter database design allowed for enrollment of patients with a wide range of CD presentations from 13 surgical sites across the United States, lending increased generalizability to our findings.

CONCLUSION

Severe preoperative cervical and upper-cervical malalignments, including C1 Slope $> 14^{\circ}$, TS-CL $\geq 57^{\circ}$, and cSVA $\geq$ 40 mm, were among the strongest indicators of nonroutine discharge following surgical correction of CD. Patient-related factors such as advanced age and preoperative gait impairment as well as fusion length and number of in-hospital complications were also associated with nonroutine discharge, and they should be taken into account to improve current preoperative risk-stratification strategies. Future large-scale studies controlling for covariates are necessary to confirm these findings; however, in identifying potential indicators of nonhome discharge following CD-corrective surgery, this study may serve as a resource for patients and surgeons to better estimate the likelihood of requiring additional health care services after surgery

Disclosures

The International Spine Study Group (ISSG) is funded through research grants from DePuy Synthes and individual donations. Dr Passias is a consultant for Medicrea and Spinewave, is on the Scientific Advisory Board for Allosource, is a teacher/speaker for Zimmer Biomet and Globus, has a grant from CSRS, and is involved in a research study for Aesculap. Dr Lafage has stock ownership in and is on the Board of Directors for Nemaris, is a teacher/speaker for DePuy Synthes, Nuvasive, K2M, and Medtronic. Dr Smith receives royalties from Zimmer Biomet, is a consultant for Zimmer Biomet, Nuvasive, and Cerapedics, is a teacher/speaker for Zimmer Biomet, Nuvasive, and K2M, and receives fellowship support from AOSpine and NREF. Dr Mundis Jr receives royalties from K2M and is a consultant for K2M, DePuy Synthes, and Nuvasive. Dr Kelly receives research support from DePuy Synthes, Oref, CSRS, AOSpine, the Fox Family Foundation, and the Barnes Jewish Foundation. Dr Protopsaltis is a consultant for Globus, Medicrea, and Innovasis, and receives research support from Zimmer Biomet. Dr Sciubba is a consultant for Medtronic and has stock ownership in DePuy Synthes, Stryker, K2M, and NuVasive. Dr Klineberg is a consultant for DePuy Synthes, Stryker, Springer, and Trevana, receives honoraria from AOSpine and K2M, and has fellowship support from AOSpine. Dr Burton is a consultant for DePuy Synthes and Allosource and is a patent holder with DePuy Synthes. Dr Hart is a consultant for DePuy Synthes, Globus, and Medtronic, is a teacher/speaker for DePuy Synthes, receives research support from Medtronic, and has other financial support from Seaspine. Dr Schwab is a speaker/teacher, consultant, and has royalties/patents with Zimmer Biomet, NuVasvie, K2M, MSD, is a teacher/speaker and consultant for Medicrea, and is a shareholder and on the Board of Directors for Nemaris. Dr Bess is a consultant for K2M and AlloSource, receives royalties from Pionee, Innovasis, K2M, Nuvasive, and DePuy Synthes Spine, and receives research support from K2M, Innovasis, Nuvasive, DePuy Synthes Spine, and Stryker. Dr Shaffrey receives royalties from, holds patents with, and consults for Medtronic, Nuvasive, and Zimmer Biomet, is a stock holder in Nuvasive, is a consultant for K2M, Stryker, and InVivo, and has grants from NIG, the Department of Defense, ISSG, DePuy Synthes, and AOSPine. Dr Ames is a consultant for DePuy Synthes, Medtronic, and Stryker, has royalties from Stryker and Zimmer Biomet, and holds patents with Fish & Richardson, PC.

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Reoperation for Proximal Adjacent Segment Pathology in Posterior Cervical Fusion Constructs that Fuse to C2 vs C3

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Received, June 16, 2018.
Accepted, January 30, 2019.
Published Online, March 12, 2019.

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BACKGROUND: Few studies have described rates of proximal clinical adjacent segment pathology (CASP) after posterior cervical decompression and fusion (PCDF).
OBJECTIVE: To investigate rates of proximal CASP at C2 vs C3 in PCDFs for degenerative spine disease.
METHODS: A retrospective review of 380 cases of PCDF for degenerative disease with proximal constructs ending at C2 vs C3 was performed. Minimum follow-up was 12 mo. The primary outcome was proximal CASP requiring reoperation. Variable analysis included demographic, operative, and complication data.
RESULTS: There were 119 patients in the C2 group and 261 in the C3 group with no significant differences in age, gender, comorbidities, presenting symptoms, or complications. Vertebral artery injury rates were 0.8% in the C2 group and 0.0% in the C3 group ($P = .12$). No patients in the C2 group had reoperation for proximal CASP, while 5.0% of patients in the C3 group did ($P = .01$). Patients with arthrodesis up to C3 had an increased risk of proximal failure when the fusion construct crossed the cervicothoracic junction ($P = .03$). Multivariate logistic regression analysis showed no factors that were independently associated with re-instrumentation for proximal CASP.
CONCLUSION: Instrumenting to the C2 level reduces the risk for proximal CASP compared to fusion only up to C3. The type of instrumentation used at these 2 levels, form of ASP disease at C1-C2, and natural motion of the relevant proximal adjacent joint may contribute to this difference. Furthermore, within the C3 cohort, fusion across the cervicothoracic junction increased the risk for proximal CASP.

KEY WORDS: Proximal clinical adjacent segment pathology, C2 pedicle screw, C3 lateral mass, Cervicothoracic junction

Neurosurgery 85:E520–E526, 2019 DOI:10.1093/neuros/nyz019 www.neurosurgery-online.com

Degenerative cervical spine disease is a common condition that may be associated with devastating outcomes such as myelopathy and paraplegia.[1] For symptomatic degenerative disease, surgery is considered superior to nonoperative management.[2] Surgical fusion, however, can result in adjacent segment pathology (ASP): significant degradation in the vertebral levels adjacent to a fusion that leads to clinically significant radiculopathy or myelopathy.[3,4] Although the exact pathophysiology of ASP remains to be fully elucidated, ASP has become a well-documented long-term complication of spine fusion.[5] The cervical spine is especially challenging due to its large amount of natural motion, particularly in the rostral (proximal) region where half of all cervical movement occurs.[4,6]

ABBREVIATIONS: **ACDF,** anterior cervical discectomy and fusion; **CASP,** clinical adjacent segment pathology; **CTJ,** cervicothoracic junction; **PCDF,** posterior cervical decompression and fusion

Most reports of ASP within the cervical spine have focused on anterior cervical discectomy and fusion (ACDF),[5] with incidences ranging from 2.4 to 2.9%[7,8] and as many as 2/3 of these requiring reoperations due to recurrence of clinical symptoms.[7] The majority of cervical fusions are performed between the C3-C7 levels,[4] and most cases of ASP have been reported to occur in the caudal C5-C7 region.[9]

To date, few studies have described rates of rostral (proximal) ASP after posterior cervical decompression and fusion (PCDF).

In PCDFs, surgeons must balance length of construct and stability with preserving sufficient range of motion. The construct length is especially important to determine since the cervical spine is a highly mobile spinal segment where increased construct length ensures more rigid fixation but also reduces patient mobility.[10] Furthermore, in the rostral cervical spine, surgeons must weigh the risks and benefits of ending a posterior cervical construct at C2 vs C3. Although C2 pedicle screws are stronger biomechanically than C3 lateral mass screws,[11,12] they can be more technically challenging to place given variable vertebral artery anatomy.[13-15] As cervical spine surgeries increase in frequency,[16,17] the long-term consequences of fusion procedures become increasingly important to understand. Here, we compare the rates of clinical ASP (CASP) in posterior cervical constructs ending in C2 cervical pedicle screws vs C3 lateral mass screws.

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METHODS

Study Design and Patient Selection

This study received institutional review board approval. Medical records were retrospectively reviewed for all neurosurgical patients at a single institution undergoing posterior cervical fusion up to C2 or C3 between 2003 and 2013. Patient consent was not obtained due to the retrospective nature of this study. Inclusion criteria were (1) patients over 18 yr of age, (2) patients undergoing posterior fusion for degenerative spine disease, (3) fusions using C3 lateral mass screws and/or C2 cervical pedicle screws as the proximal ends of the construct, and (4) patients with at least 12 mo of follow-up. In the cervical spine, all instrumented levels were fused at the lateral masses except for at the C2 level. Furthermore, the C7 level would not be instrumented if the cervicothoracic junction (CTJ) was crossed and thoracic levels were fused. All index and revision surgeries were performed posteriorly. In general, surgical decompression and fusion was performed by first exposing bony anatomy and drilling pockets for screw placement. Then, decompression of the spinal cord was performed before placing instrumentation, decorticating and fusing with or without autograft and allograft, and finally closure in multiple layers. Postoperatively, all patients with degenerative spine disease received a computed tomography scan but magnetic resonance imaging was reserved for those who developed new neurological problems.

Variables

General patient characteristics including age, gender, comorbid conditions, history of previous cervical spine surgery, presenting symptoms, and preoperative Nurick scores were gathered from the attending surgeon's clinical notes. Operative parameters such as number of decompressed levels by laminectomy, number of fused levels, use of allograft, perioperative complications, and length of stay were obtained from operative and clinical notes. Parameters such as spondylolisthesis were only denoted in a patient if they were present within the patient's range of operated levels. The most recent surgical note was considered the last date of follow-up. Patients with insufficient follow-up were contacted by phone for updates. The primary outcome variable was reoperation for proximal CASP. Secondary outcome measures included perioperative complications and reoperation for distal CASP.

Statistical Analysis

For data analysis, 2 cohorts were established: (1) a group in which the most rostral instrumentation ended at C2 (with a C2 pedicle screw) and (2) a group in which the most proximal instrumentation ended at C3 (with a lateral mass screw). This allowed for comparison of rates of reoperation for proximal CASP. All personal data were de-identified throughout analysis. Variable analysis included demographic, operative, and complication data. Independent *t*-tests or Fisher's exact tests were used to compare the 2 cohorts where appropriate. For each test, patients with the relevant missing data were excluded. Subanalyses were conducted on proximal CASP by controlling for fusions that crossed the CTJ or not. Similar outcomes analyses were conducted for distal CASP. A multivariate logistical regression analysis was performed to identify independent factors associated with proximal CASP. All analyses were performed in STATA SE 12 (StataCorp, College Station, Texas), and statistical significance was defined as $P \leq .05$.

RESULTS

Participants and Descriptive Data

During the study period, 576 adult patients underwent a PCDF for degenerative spine disease. A total of 380 patients met the inclusion criteria, with 119 patients (31.3%) in the C2 group and 261 patients (68.7%) in the C3 group (Table 1). The mean age at surgery was 63.4 ± 10.9 yr for all patients ($P = .53$) and 64.0% of patients were males ($P = .98$). The average follow-up time for all patients was 49.1 ± 28.8 mo (47.7 mo in the C2 group and 49.8 mo in the C3 group, $P = .51$). The 2 most common preoperative signs were myelopathy (91.6% in the C2 group and 93.1% in the C3 group, $P = .60$) and axial neck pain (58.0 and 55.2%, $P = .61$).

The average preoperative Nurick score was not significantly different between groups ($P = .25$), with an average and standard deviation of 2.1 ± 1.2 in both cohorts. Preoperative comorbidities were also not statistically different, including diabetes (22.7% in the C2 group and 19.9% in the C3 group, $P = .55$) and osteoporosis (4.2% in the C2 group and 6.9% in the C3 group, $P = .30$). Of all patients, 23.4% had a history of previous anterior cervical fusion (21.0% in the C2 group vs 24.5% in the C3 group, $P = .45$) and 6.3% had a history of previous posterior fusion (5.0% in the C2 group and 6.9% in the C3 group, $P = .49$).

Operative Parameters

There were 21 patients (17.6%) in the C2 group who had associated ossification of the posterior longitudinal ligament, compared to 20 patients (7.7%) in the C3 group ($P = .003$; Table 2). Additionally, a significantly higher proportion of patients in the C2 group had associated spondylolisthesis (26.1 vs 10.7%, $P < .001$). The average number of decompressed and fused levels was higher in the C2 group ($P < .001$). However, this difference in the number of levels decompressed by laminectomy

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TABLE 1. General Patient Demographics of Patients Undergoing PCDFs that Fuse up to C2 or C3

	C2	C3	*P* value
Patient demographics			
No. of cases	119	261	
Age at surgery (mean years)	63.9 ± 10.4	63.1 ± 11.2	.53
Average follow-up time (mean months)	47.7 ± 28.2	49.8 ± 29.1	.51
Male gender	76 (63.8%)	167 (64.0%)	.98
Presenting symptoms			
Neck pain	69 (58.0%)	144 (55.2%)	.61
Headache	13 (10.9%)	27 (10.3%)	.87
Radiculopathy	32 (26.9%)	49 (18.8%)	.08
Myelopathy	109 (91.6%)	243 (93.1%)	.60
Weakness	96 (80.7%)	188 (72.0%)	.07
Sensory	79 (66.4%)	163 (62.5%)	.46
Gait	80 (67.2%)	185 (70.9%)	.51
Bladder	17 (14.3%)	35 (13.4%)	.80
Preop Nurick (mean)	2.1 ± 1.2	2.1 ± 1.2	.25
Comorbidities			
Diabetes (%)	27 (22.7%)	52 (19.9%)	.55
Osteoporosis (%)	5 (4.2%)	18 (6.9%)	.30
Obesity (%)	17 (14.3%)	21 (8.0%)	.06
Smoking (%)	28 (23.5%)	62 (23.8%)	.09
Previous PCDF (%)	6 (5.0%)	18 (6.9%)	.49
Previous ACDF (%)	25 (21.0%)	64 (24.5%)	.45

PCDF, posterior cervical decompression and fusion; ACDF, anterior cervical decompression and fusion.
*Indicates statistical significance ($P < .05$).

was not greater than 1.0 when compared to the C3 group (average difference in decompressed levels was 0.7) where instrumentation occurred only up C3. The difference in number of fused levels, however, was greater than 1 (average difference in fused levels was 1.7). Distally, 67/119 (56.3%) cases in the C2 cohort crossed the CTJ, while 66/261 cases (25.3%) did so in the C3 cohort ($P < .001$).

The rates of perioperative complications were not significantly different between groups. There was one case of vertebral artery injury (0.9%) in the C2 group compared to zero in the C3 group ($P = .12$). The most common complication was wound infection, which occurred in 5.3% of all patients: 4.2% in the C2 group and 5.7% in the C3 group ($P = .51$). This was followed by incidental durotomy in 4.0% of all patients, with 3.4% of patients in the C2 group and 4.2% in the C3 group ($P = .68$). The average length of stay was 6.4 ± 4.6 d for patients in the C2 group and 5.5 ± 3.8 d for patients in the C3 group ($P = .07$), approaching but not reaching statistical significance.

Outcomes

Within each group, the average postoperative Nurick scores were significantly improved from their respective preoperative scores ($P < .001$) with the average postoperative Nurick score being 1.3 in both the C2 and C3 groups (Table 3). However, there was no difference in the average improvement in Nurick scores between the 2 groups (C2 = –0.8, C3 = –0.8, $P = .87$).

No patients in the C2 cohort but 13 patients in the C3 cohort (5.0%) had re-instrumentation for proximal CASP ($P = .01$; Table 4). The average time from index operation to reoperation for proximal CASP was 49.8 ± 38.6 (range 21.4-106.1) mo. Within the C3 cohort that had revision surgery, 7/66 cases (10.6%) crossed the CTJ while 6/195 cases (3.1%) did not cross the CTJ ($P = .03$). Multivariate logistic regression analysis involving gender, smoking status, number of levels decompressed, and number of levels fused showed no factors that were independently associated with re-instrumentation for proximal CASP (Table 5).

Distally, 8 patients in the C2 cohort (6.7%) and 19 in the C3 cohort (7.9%) required reoperations for CASP ($P = 1.00$). Stratifying by fusion across the CTJ, distal revisions occurred in 5/133 cases that fused crossed the CTJ (3.8%) and 22/247 cases (8.9%) that did not ($P = .09$).

DISCUSSION

Surgical management is superior to conservative treatment for symptomatic degenerative cervical spine disease.[2] However, fusion leads to a risk for CASP.[5] In posterior cervical fusions, the rates of proximal CASP are unknown and surgeons must decide whether it is beneficial to extend a fusion construct past C3 into C2. The 2 endpoints involve differences in both the types of screws used and adjacent joint motions involved

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TABLE 2. Intraoperative Parameters, Perioperative Parameters, and Comorbidities for Posterior Cervical Decompression and Fusions

Parameter	C2	C3	*P* value
No. of cases	119	261	
Number of decompressed[a] levels (mean)	4.3 ± 1.5	3.6 ± 1.5	<.001*
Number of fused levels (mean)	6.1 ± 1.5	4.4 ± 1.2	<.001*
Spondylolisthesis	31 (26.1%)	28 (10.7%)	<.001*
OPLL	21 (17.6%)	20 (7.7%)	<.01*
Foraminal stenosis	22 (18.5%)	53 (20.3%)	.74
BMP use	8 (6.7%)	19 (7.3%)	.85
Allograft	102 (85.7%)	211 (80.8%)	.25
Vertebral artery injury	1 (0.8%)	0	.12
Durotomy	4 (3.4%)	11 (4.2%)	.68
Postop CSF leak	0	2 (0.8%)	.34
Hematoma	1 (0.8%)	2 (0.8%)	.94
Wound infection	5 (4.2%)	15 (5.7%)	.51
Wound dehiscence	5 (4.2%)	10 (3.8%)	.86
Length of stay (mean days)	6.4 ± 4.6	5.5 ± 3.8	.07

OPLL, ossification of the posterior longitudinal ligament; BMP, bone morphogenetic protein; CSF, cerebrospinal fluid.
[a] Decompression by laminectomy.
*Indicates statistical significance ($P < .05$).

TABLE 3. Postoperative Outcomes of Patients Undergoing Posterior Cervical Decompression and Fusion that Fuse up to C2 or C3

Parameter	C2	C3	*P* value
No. of cases	119	261	
Symptoms at last follow-up			
Neck pain (%)	29 (24.4%)	77 (29.5%)	.26
Headache (%)	8 (6.7%)	11 (4.2%)	.31
Radiculopathy (%)	11 (9.2%)	18 (6.9%)	.45
Myelopathy (%)	42 (35.3%)	123 (47.1%)	.03*
Weakness (%)	34 (28.6%)	81 (31.0%)	.57
Sensory (%)	25 (21.0%)	72 (27.6%)	.15
Gait (%)	28 (23.5%)	83 (31.8%)	.11
Bladder (%)	1 (0.8%)	8 (3.1%)	.18
Postop Nurick	1.3 ± 1.4	1.3 ± 1.5	.35
Surgery for clinical adjacent segment pathology (%)	0	13 (5.0%)	.01*

*Indicates statistical significance ($P < .05$).

and these factors may preferentially contribute to proximal CASP. This study evaluated rates of proximal CASP in fusions extending up to C2 instrumented with cervical pedicle screws compared to fusions instrumented up to C3 with lateral mass screws.

Overall, C2 pedicle screw instrumentation showed a lower rate of reoperation for proximal CASP, which is consistent with cadaveric biomechanical models that suggest pedicle screws are more stable and have greater pullout strength than lateral mass screws. Usually, 24 to 30 mm pedicle screws are used for the C2 level while 12 to 14 mm lateral mass screws are used for C3.[18,19] This difference has led to speculation that C2 pedicle screws are more stable and result in fewer long-term complications: numerous biomechanical studies show that pedicle screws can resist greater forces than lateral mass screws before pullout and failure.[12,20-22] A pedicle screw inserted into C2 can resist an average of 650 N of force before being pulled out compared to a lateral mass screw in C3 that can resist 391 N.[12] This mechanical superiority has been, in part, attributed to pedicle screws' increased length and therefore purchase in both cortical and cancellous bones.[12,23]

Fusing up to C2 vs C3 also changes the natural motion of the relevant proximal joint. The C1-C2 joint involves primarily rotational motion and contributes to nearly half of neck rotation, while the C2-C3 joint exhibits both rotational and lateral bending movements.[6,10] C1-C2 is a highly mobile

TABLE 4. Details of C3 Group Patients Requiring Revision Surgery

Case no.	Initial surgery[a]	Age of initial surgery (years)	Clinical indicators for revision[c]	Time to revision (months)	Revision surgery	Follow-up after revision surgery (months)	Current symptoms
1	C3-C7 F	73.6	PJK,P	43.6	C2-C7 F	19.9	Neck pain
2	C3-C7 F, C3-C6 D	52.5	PJK, M,S,G,P	21.4	C2-T2 F	4.9	Neck pain, numbness
3	C3-C6 F, C3-C6 D	50.1	PJK, M,S,P	106.1	C2-T2 F	16.8	Continued weakness
4	C3-T2 F, C3-C7 D	60.5	PJK, M,S,G,P	28.3	C2-T2 F	30.8	Occasional BLE paresthesias
5	C3-T2 F, C3-C7 D	69.3	PS,P	17.4	C2-T2 F	35.2	Neck pain
6	C3-T2 F, C7-T1 D[b]	41.9	PS,M,S,P	24.1	C2-T2 F	26.0	Brisk BLE/BUE reflexes
7	C3-T2 F, C4-C7 D	52.8	PS, M,S,G,P	20.7	C2-T2 F	18.6	Neck pain, hand numbness, gait difficulty
8	C3-C6 F, C3-C6 D	61.4	PIF,P	6.5	C2-T2 F	65.6	Doing well
9	C3-C7 F, C3-C6 D	63.7	PIF,S,P	21.2	C2-T2 F	16.4	Neck pain
10	C3-C7 F, C4-C7 D	56.7	PIF, M,S,G,P	7.5	C2-T2 F	8.5	Doing well
11	C3-T2 F, C3-C7 D	60.5	PIF,S,P	16.8	C2-T2 F	23.5	Occasional numbness
12	C3-T2 F, C3-C7 D	64.0	PIF, M,G,P	14.3	O-T2[d] F	19.9	Continued BUE weakness
13	C3-T2 F, C4-C7 D	72.5	PIF,M,S	12.1	C2-T2 F	17.2	Doing well

[a]F = fusion, D = decompression (laminectomy).
[b]D = foraminotomy.
[c]PJK = proximal junctional kyphosis, PS = pseudarthrosis, IF = instrumentation failure, M = motor deficits, S = sensory deficits (numbness, tingling, etc.), G = gait instability, P = pain (neck pain, radiculopathy).
[d]Patient had prior O-C2 fusion which also failed.
BLE = bilateral lower extremity, BUE = bilateral upper extremity
*Indicates statistical significance ($P < .05$).

TABLE 5. Binomial Logistic Regression Analysis for Proximal CASP Surgery

Independent variable	Odds ratio	*P* value	95% Confidence interval	
Male gender	2.322	.49	0.217	24.793
Smoking	1.054	.96	0.105	10.631
No. of levels decompressed	0.819	.50	0.461	1.453
No. of levels fused	1.636	.27	0.680	3.934

CASP, clinical adjacent segment pathology.
Two independent variables, "Fusion to C2" and "Preoperative Spondylolisthesis", were omitted from this binomial logistic regression due to being perfectly correlated with proximal CASP surgery. No reoperations for proximal CASP occurred in the "Fusion to C2" or "Preoperative Spondylolisthesis" patients.

joint but is distinctly different from the subaxial spine (including C2-C3) because of its limited lateral bending activity.[10] This difference in kinetics at C2-C3 may contribute to the higher rate of reoperation for proximal CASP that was found in this study's C3 cohort. In biomechanical studies, increased motion contributes to adjacent level degeneration: increased adjacent segment motion and elevated intradiscal pressures have been found after cervical fusion.[24,25] However, few studies on arthrodesis and its effects on adjacent levels have focused on only the upper cervical spine and those that do have included occipitocervical fusion.[6] One study by Schwab et al. found in C2-T1 cadaveric specimens that significant motion instability occurs above C3-C4 fusions but could not evaluate the effects of C2-C3 fusions on C1-C2 motion since they used specimens without C1.[25] In our study, lower rates of reoperation for proximal CASP occurred in fusions up to C2 compared to C3. This finding suggests that despite C1-C2's range of natural motion, the actual type of movement may also be important. In fusions up to C3, both rotational and lateral bending activities occur together in the adjacent C2-C3 joint whereas in fusions up to C2, mainly rotational activity occurs in the adjacent C1-C2 joint.

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The number of levels fused was also different between the 2 cohorts: on average, the C2 cohort had more levels fused than the C3 cohort. Considering the C2 cohort had a lower rate of CASP requiring revision surgery, this study's finding may seem inconsistent with most reports that longer fusions increase the risk for adjacent segment degeneration.[26,27] Larger lever arms increase biomechanical strain on the distal and proximal ends of a fusion construct and accelerate adjacent segment degeneration.[26] However, our findings may be explained by both the stability provided by the C2 pedicle and natural course of adjacent disease at the C1-C2 junction. Proximally, the C2 pars and pedicle provide a long cortically lined frame for screw placement and thereby provide a strong proximal anchor point to limit motion. Further, C1-C2 ASP is a rare phenomenon and, when it does occur, may be related to increased facet arthrosis after adjacent fusions.[28,29] It is important to note, however, that patients with fusions extending up to C3 with constructs that crossed the CTJ had a significantly higher rate of revision surgery for proximal CASP (10.6% vs 3.1%, $P = .03$) compared to those that did not cross the CTJ. Fusing past the CTJ thus does appear to increase degeneration at the C2-C3 level, likely because of the longer construct and therefore greater lever arms and forces involved.

Perioperative Complications

Early postoperative complication rates were similar between the C2 and C3 groups. Wound infection was the most common complication at 5.3% overall although there was no difference between groups. This infection rate is slightly higher but largely consistent with the 1.3 to 4.6% range that has been reported earlier.[30] Incidental durotomy was also a common complication in this study at 4.0%, which resembles the 3.85% rate found by Guerin et al. across all types of spine surgeries in 1326 patients.[31] Additionally, vertebral artery injury is a common concern for pedicle screws due to their risk of breaching the transverse foramina.[11,15,32] Although several papers in the literature state that cervical pedicle screws have a higher risk of injuring the vertebral artery than lateral mass screws,[22,33,34] this study did not find a statistically significant difference in vertebral artery injury between the C2 pedicle screw and C3 lateral mass screw cohorts.

Limitations

This study has several limitations. First, this is a retrospective study and is therefore inherently limited by factors including confounding by unmeasured variables. Information bias is also possible since patient-reported complaints were evaluated based on clinical notes and not on more objective measures. Second, radiographic analysis was not evaluated since this study was interested in reoperation rates for CASP rather than radiological pathology. The decision to fuse to either C2 or C3 is dependent on each individual patient's case but long-term clinical planning should consider a possible increased risk for proximal CASP in fusions to C3, especially those that cross the CTJ. To further evaluate the significance of these findings, a larger prospective study should be conducted.

CONCLUSION

Proximal (rostral) CASP in the cervical spine in the context of posterior cervical fusions is not well described in the literature. This study sought to evaluate whether instrumenting to C2 in posterior fusions impacts reoperation rates for proximal CASP. We demonstrate that fusing to C2 reduces the risk for proximal CASP compared to fusion to only C3, especially for constructs that cross the CTJ. Factors contributing to this difference may include the superior biomechanical strength of the C2 pedicle screw, natural course of ASP disease at C1-C2, and intrinsic differences in motion between the C1-C2 joint compared with the C2-C3 joint.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors performed a retrospective review of 380 patients who had undergone posterior cervical fusion with proximal constructs ending at either C2 or C3. With an average follow-up of approximately 4 years, they found that 5% of patient in the C3 UIV group and 0% of patients in the C2 UIV required revision surgery for proximal adjacent segment pathology. In addition, within the C3 UIV group, patients with distal construct crossing the cervicothoracic junction (CTJ) had a higher likelihood of developing proximal junctional pathology 10.6% (crossing CTJ) vs 3.1% (not crossing CTJ). This study provides helpful insights regarding rate of proximal adjacent level degeneration, which is what one would expect from biomechanical standpoint (ie, stiffer construct leads to higher likelihood of adjacent level degeneration). In addition, this study also demonstrated that there was a trend toward more distal revision surgery in posterior cervical constructs NOT crossing CTJ (8.9%) vs crossing CTJ (3.8%), even though it did not reach statistical significance in this study ($P = .09$).

Ultimately, the decision on whether to include C2 in the construct or whether to cross the CTJ during posterior cervical fusion depends on many factors, including the particular pathology being treated, patient age, medical comorbidity, cervical alignment, surgeon preference, patient expectation, and many other factors. The findings from this study are valuable in helping spine surgeons and patients to make educated decisions regarding the optimal surgical plan.

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This study exposes a critical issue with 5% of patients in the C3 UIV group and 0% in the C2 UIV requiring revision surgery for proximal adjacent segment pathology. Proximal adjacent segment pathology worsened significantly with crossing the cervicothoracic junction. It is time we added the C2 segment to fusions to the cervicothoracic junction with the UIV slated to be C3. The added stress to the solitary C2-3 level leads to high failure and revision rate. There is very little additional loss of motion extending to C2 or decrease in patient reported outcomes.

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Clinicopathological and Prognostic Characteristics in Extra-Axial Chordomas: An Integrative Analysis of 86 Cases and Comparison With Axial Chordomas

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Received, May 15, 2018.
Accepted, February 14, 2019.
Published Online, March 20, 2019.

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BACKGROUND: Currently, clinical characteristics and prognostic factors of extra-axial chordoma (EAC) remain poorly understood.
OBJECTIVE: To characterize clinicopathological characteristics in a large EAC cohort and investigate their correlation with survival. We also attempted to compare these outcomes with axial chordoma (AC).
METHODS: Medline and Embase searches (from inception to February 28, 2018) were conducted to identify eligible studies as per predefined criteria. The local database at our center was also retrospectively reviewed to include additional patients.
RESULTS: Forty-three studies from the literature and 86 patients from our local institute were identified, resulting in a total of 86 EAC patients and 75 AC patients for analysis. Overall, EAC had similar characteristics to AC, except for having higher CAM5.2 expression, common lobular growth pattern, and better prognosis. Whereas wide surgical resection was consistently associated with favorable survival in both EAC and AC cohorts on univariate analyses, most parameters showed differential prognostic implications between the 2 groups. Significant prognostic factors for local recurrence-free survival on multivariate analysis included type of surgery in both cohorts and tumor Brachyury expression and adjuvant radiotherapy in AC cohort. Multivariate analysis of overall survival demonstrated that type of surgery, tumor Brachyury expression, and duration of symptoms were significant predictors in the AC cohort, whereas none of the analyzed parameters were predictive of overall survival for the EAC group.
CONCLUSION: These data suggest potentially distinct biological behaviors between EAC and AC and may provide useful information to better understand the prognostic characteristics and improve the outcome prediction of EAC patients.

KEY WORDS: Extra-axial chordoma, Axial chordoma, Spine, Skull base, Prognostic factors, Survival, Comparative study

Neurosurgery 85:E527–E542, 2019 DOI:10.1093/neuros/nyz073 www.neurosurgery-online.com

Chordoma is a very rare malignant mesenchymal tumor that is thought to originate from remnants of the embryonic notochord.[1,2] Chordoma is a low-grade malignancy that grows slowly[3] and is usually diagnosed after a long clinical course. The annual incidence of chordoma is approximately less than 1 case per million people.[4,5] Clinically, chordoma is resistant to traditional chemotherapy and radiotherapy. At present, the standard care for chordoma is complete surgical resection, followed by optional adjuvant radiotherapy,[6-9] which provides the best chance of long-term disease control.[10]

Chordoma occurs almost exclusively in the axial skeleton. The most common location is the spine and the skull base region.[11] As such, many associated studies are focused on spinal chordoma or skull base chordoma (SBC), and these studies have contributed to a better understanding of chordoma progression and prognosis.

ABBREVIATIONS: AC, axial chordoma; **EAC,** extra-axial chordoma; **EMA,** epithelial membrane antigen; **LRFS,** local recurrence-free survival; **OS,** overall survival; **SBC,** skull base chordoma

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For example, it has been suggested that the type of surgical resection, a patient's age, pathological chordoma type, and the extent of tumor invasion are significant predictors of patient survival in spinal chordoma.[9,12] Similarly, in SBC, previous studies have found that incomplete or intralesional tumor resection, recurrent disease, lack of postoperative radiotherapy, and classic chordoma type are associated with poor patient outcome.[13-15] In addition, published data also provide accumulating evidence for the use of molecular biomarkers in predicting spinal chordoma and SBC prognosis.[15,16] Collectively, these findings provide useful information for prognostic risk stratification and outcome prediction, as well as for the development of novel therapeutic strategies in patients with axial chordoma (AC).

However, despite being very uncommon in clinical practice, chordoma can also initially develop in extra-axial regions. In such situations, common sites for chordoma occurrence may include the nasopharynx, posterior mediastinum, appendicular skeleton, and soft tissues. Currently, the precise mechanism underlying extra-axial chordoma (EAC) development is not well known. Previous studies have suggested that EAC may arise from the ectopic notochordal tissues located in extra-axial areas or may be caused by a molecular mechanism unrelated to the notochordal origin.[17] To date, although studies on EAC have been reported in the literature, most of them are anecdotal cases or small case series. Therefore, the detailed clinicopathological characteristics of EAC remain poorly understood, and there is currently a lack of data discussing the complete range of prognostic factors for EAC. In this study, we aimed to perform an integrative analysis of a large number of EAC cases and to characterize the clinicopathological parameters and their correlation with local recurrence-free survival (LRFS) and overall survival (OS) of patients. We also attempted to compare the clinical and prognostic characteristics between patients with EAC and those with AC.

METHODS

Literature Review

An electronic literature search from the inception to February 28, 2018 was performed using Medline and Embase databases. The keyword combinations used for searching were "chordoma" or "chordomas"; "extra-axial"; "extranotochordal"; "ectopic"; "chordoid"; "peripheric um" or "peripheral"; "appendicular skeleton"; "ilium"; "soft tissue" or "soft tissues"; "mediastinal" or "mediastinum"; "nasopharynx," "nose," or "nasal"; "parapharyngeal" or "pharyngeal"; "nasopharyngeal," "naso-oropharyngeal," "oropharyngeal," "nasooropharyngeal," or "oropharynx"; "parachordoma" or "parachordomas", "chordomalike tumor" or "chordoma-like tumor". Figure 1 summarizes the detailed search algorithm.

We included studies that addressed primary chordoma cases occurring initially outside the axial skeleton, irrespective of whether they invaded the axial skeleton or not. To date, chordomas that arise in extra-axial sites are usually termed parachordomas in the literature.[17,18] As parachordomas may represent other lesions (such as extraskeletal myxoid chondrosarcoma or myoepithelioma/parachordoma) instead of true chordomas,[17] these cases were included only when they had positive Brachyury immunostaining, as this protein has been suggested as a reliable marker in confirming the identity of parachordomas as true EACs and excluding lesions with similar histological and immunohistochemical features.[17,18] Bibliographies of the relevant studies were manually examined to identify any additional eligible records. Studies were restricted to those written and published in English and involving humans. The criteria for study exclusion were as follows: no EAC cases discussed or EAC developed after previous AC, survival data for individual patients were not specified, duplicate publications, surgical tumor resection was not performed, and failing to provide any patient information.

Two reviewers independently selected eligible studies according to the inclusion criteria and extracted data from each study. These data included the following: patient characteristics (age, sex, and duration of symptoms), tumor clinicopathological features (location; size; extent of invasion; presence or absence of lobular growth pattern; immunohistochemical expression of Brachyury, pan-cytokeratin, CAM5.2 [cytokeratin 8], cytokeratin 19, S-100, vimentin, and epithelial membrane antigen [EMA]); treatments (wide or subtotal surgical resection, radiation, and/or chemotherapy), endpoint events (local recurrence and death), and time to critical events. Lobular growth pattern of the tumors was evaluated as previously suggested (Figure 2).[19] The primary data were LRFS, defined as the interval from tumor resection to the diagnosis of the first local recurrence, and OS, which was measured as the interval from the date of surgery to death from any cause. Discrepancies were resolved between 2 authors through consensus. For analysis, the data of patient age ($\leq$55 yr or >55 yr) and tumor size ($\leq$5 cm or > 5 cm) were separated into 2 groups as previously suggested.[20,21] Expression of the proteins on chordoma cells was scored as high when strong or diffuse immunostaining was described in the publication and low if it was recorded otherwise.

Local Cohort

A retrospective search of the institutional pathology database was performed to identify eligible chordoma cases at our center. This procedure was approved by our hospital ethical committee, and informed consent was obtained from each patient before commencing the study. The study protocol was approved by the Institutional Review Board at the Second Xiangya Hospital of Central South University, Hunan, P.R. China. Written informed consent was obtained from each patient for publication of this study. A total of 11 patients with EAC who were surgically treated at our institute between December 2003 and December 2016 were identified. For comparative analysis, 75 AC patients (including 13 with SBC and 62 with spinal chordoma) who were treated between June 2002 and March 2017 were also enrolled. Fifty-four AC cases were previously described in our studies,[22-24] and the follow-up information was updated in September 2015. All other patients were followed-up with regular clinical and radiographic examinations until December 2017. Tumor diagnosis was confirmed through histological examination of hematoxylin and eosin-stained sections by 2 independent neuropathologists (Y.J. and X.L.S.) according to previously published criteria.[2] Patient and tumor characteristics, treatment history, and clinical outcomes were retrieved from patients' medical records. Observations were censored when the patient was tumor free in terms of the LRFS analysis or when the patient was alive in terms of the OS analysis.

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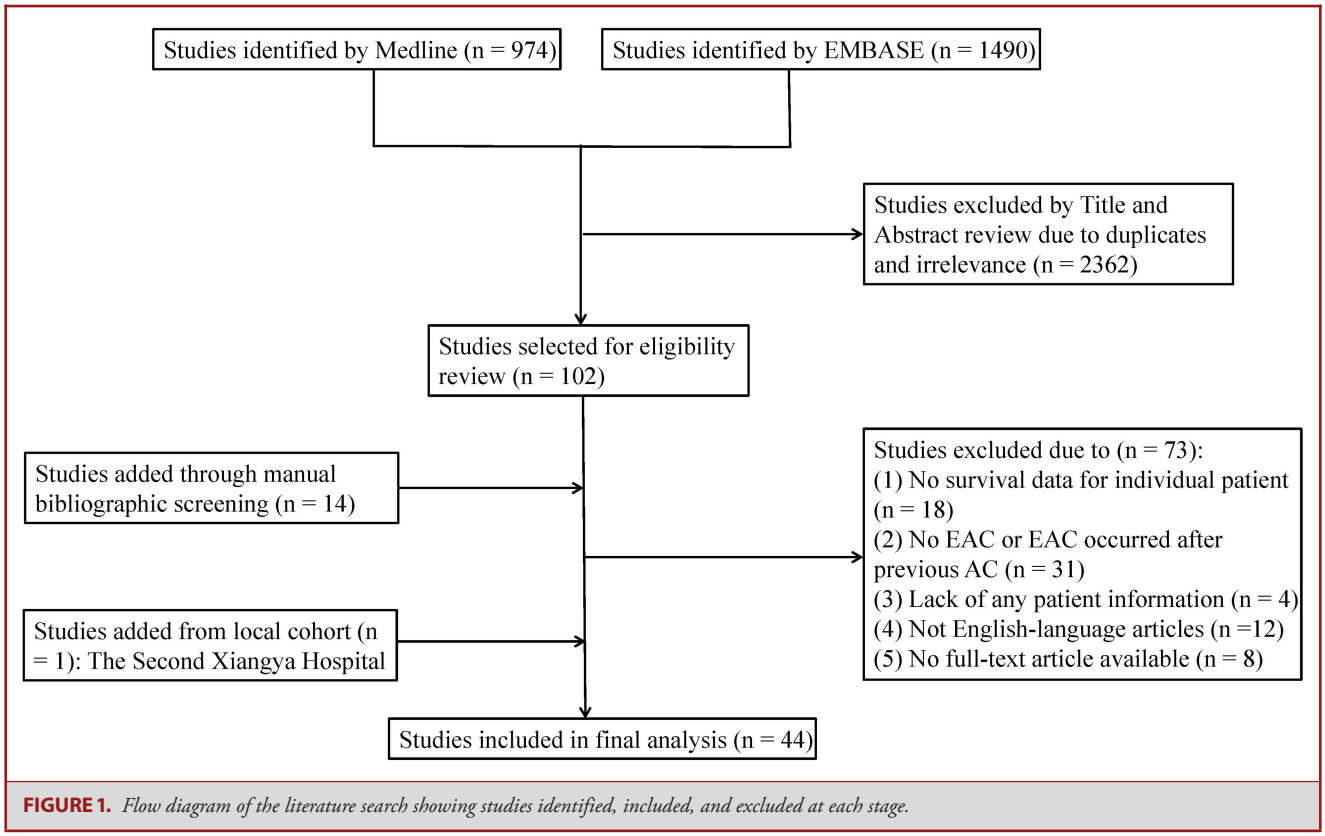


FIGURE 1. *Flow diagram of the literature search showing studies identified, included, and excluded at each stage.*

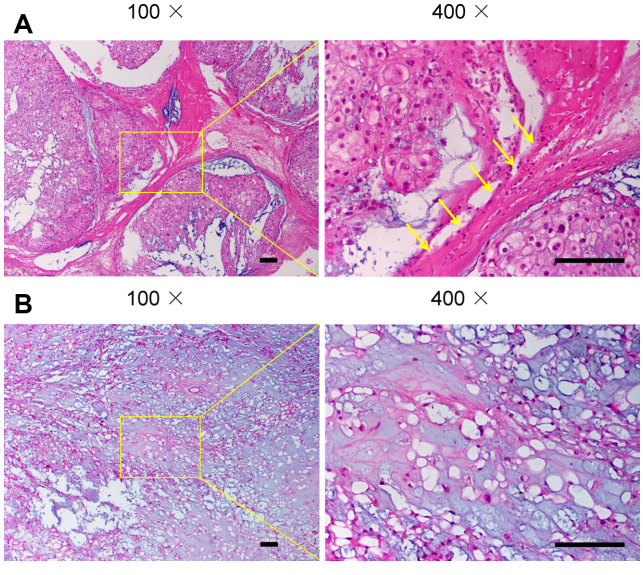


FIGURE 2. *Representative hematoxylin-eosin stained sections for chordoma cases presenting with* **A** *and without* **B** *lobular growth pattern demarcated by intralesional fibrous septum (yellow arrow). Scale bar = 100 μm.*

Immunohistochemistry Staining and Evaluation

Immunohistochemistry was performed as previously described.[22,23] Briefly, paraffin-embedded sections (4 μm) of 86 chordoma specimens from our institute were deparaffinized in xylene and rehydrated with a graded series of ethanol solutions and then rinsed in distilled water. After antigen retrieval and blocking, the tissue sections were then incubated with primary antibodies (**Supplemental Digital Content 2**) at 4°C overnight. After treatment with a secondary biotinylated goat anti-rabbit or anti-mouse immunoglobulin, sections were then incubated with a streptavidin-peroxidase conjugate (Auragene, Changsha, Hunan, China), followed by visualization with 3,3′-diaminobenzidine solution and counterstaining with hematoxylin. Immunohistochemistry results were independently assessed by 2 well-experienced neuropathologists (Y.J. and X.L.S.) who were blinded to the clinical data. For comparative analysis of local and literature data, expression of the proteins was evaluated by a similar method, and the data were divided into 2 groups: those with strong expression (the high-expression group) and those with negative and weakly or normally positive expression (the low-expression group) according to the method described above.

Statistical Analysis

All statistical analyses were performed using SPSS 17.0 (SPSS, IBM Inc, Armonk, New York). Continuous data are presented as the mean ± standard deviation and were analyzed by Student's *t*-test or one-way analysis of variance. Categorical variables were analyzed using

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TABLE 1. Comparison of Baseline Characteristics Between Literature and Local EAC Cohort (n = 86)

Variable	Categories	All (*n*)	Literature (*n*)	Local cohort (*n*)	*P* Value
Age (yr)	Continuous	86 (44.8 ± 20.4)	75 (44.5 ± 21.0)	11 (47.0 ± 16.4)	.715
Gender	Male	56	48	8	.819
	Female	30	27	3	
Duration of symptoms (mo)	Continuous	46 (30.6 ± 73.2)	35 (20.6 ± 26.0)	11 (62.4 ± 142.7)	.356
Tumor size (largest diameter, cm)	Continuous	52 (6.4 ± 4.2)	41 (6.4 ± 4.1)	11 (6.56 ± 4.65)	.906
Tumor location	Upper respiratory tract	31	29	2	**.029**
	Limbs	41	34	7	
	Thorax	11	11	0	
	Pelvic	3	1	2	
Extent of invasion	Soft tissue	43	37	6	.383
	Soft tissue and bone	25	20	5	
	Intraosseous	17	17	0	
Type of surgery	Not wide resection	29	25	4	1.000
	Wide resection	56	49	7	
Adjuvant radiotherapy	No	53	45	8	1.000
	Yes	18	15	3	
Lobular growth patterns	No	13	9	4	.347
	Yes	48	41	7	
Pan-cytokeratin expression	Low	32	25	7	.534
	High	13	9	4	
CAM5.2 expression	Low	14	9	5	.660
	High	21	15	6	
Cytokeratin 19 expression	Low	20	12	8	.904
	High	8	5	3	
S-100	Low	51	41	10	.634
	High	8	7	1	
EMA expression	Low	23	13	10	.065
	High	10	9	1	
Vimentin expression	Low	17	10	7	.953
	High	10	6	4	
Brachyury expression	Low	26	20	6	.645
	High	17	12	5	
Recurrence	No	49	44	5	.138
	Yes	22	16	6	
Dead	No	62	54	8	.769
	Yes	15	12	3	

EAC, extra-axial chordoma; EMA, epithelial membrane antigen.
Bold values indicate $P < .05$.

the Chi-square test or Wilcoxon's rank sum test, where appropriate. The Cutoff Finder web application (http://molpath.charite.de/cutoff) was applied to obtain the cutoff point for the duration of symptoms in prognosis analysis.[25] Specifically, the cutoff was determined as the value with the minimum *P* value from the log-rank test (**Supplemental Digital Content 4**), which was subsequently corrected according to a previously described method.[26] Univariate analyses of clinicopathological parameters and patient outcomes were conducted by the Kaplan–Meier method using log-rank tests. Multivariate Cox proportional hazard models were performed to identify variables that could independently predict LRFS and OS by including factors that were significant in the univariate analysis. All tests were 2-sided, and the significance level was set at a *P* value $\leq .05$.

RESULTS

Patient and Tumor Characteristics of the EAC Cohort

A total of 75 EAC patients from 43 studies (**Supplemental Digital Content 3** and **Supplemental Digital Content 1**) and 11 patients from our institute were included in this study. Overall, no statistically significant difference was observed for most of the baseline characteristics between the literature cohort and the local cohort, except for in tumor location (Table 1).

Table 1 summarizes the detailed patient and tumor characteristics of the 86 patients with EAC. The results of immunostaining for the markers varied among different studies, and the

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TABLE 2. Comparison of Baseline Characteristics between Patients With EAC ($n = 86$) and AC ($n = 75$)

Variable	Categories	All (*n*)	EAC (*n*)	AC (*n*)	*P* Value
Age (yr)	Continuous	161 (49.1 ± 18.6)	86 (44.8 ± 20.4)	75 (54.0 ± 15.0)	**.001**
Gender	Male	105	56	49	.977
	Female	56	30	26	
Duration of symptoms (mo)	Continuous	121 (26.0 ± 50.0)	46 (30.6 ± 73.2)	75 (23.1 ± 27.1)	.421
Tumor size (largest diameter, cm)	Continuous	127 (6.1 ± 3.8)	52 (6.4 ± 4.2)	75 (5.9 ± 3.5)	.438
Extent of invasion	Soft tissue without bone invasion	43	43	0	**<.001**
	Soft tissue with bone invasion	76	25	51	
	Intraosseous	41	17	24	
Type of surgery	Not wide resection	58	29	29	.550
	Wide resection	102	56	46	
Adjuvant radiotherapy	No	109	53	56	.998
	Yes	37	18	19	
Lobular growth patterns	No	60	13	47	**<.001**
	Yes	76	48	28	
Pan-cytokeratin expression	Low	90	32	58	.446
	High	30	13	17	
CAM5.2 expression	Low	73	14	59	**<.001**
	High	37	21	16	
Cytokeratin 19 expression	Low	80	20	60	.353
	High	23	8	15	
S-100	Low	111	51	60	.326
	High	23	8	15	
EMA expression	Low	83	23	60	.242
	High	25	10	15	
Vimentin expression	Low	78	17	61	.054
	High	24	10	14	
Brachyury expression	Low	61	26	35	.149
	High	57	17	40	
Recurrence	No	73	49	24	**<.001**
	Yes	73	22	51	
Dead	No	107	62	45	**.006**
	Yes	45	15	30	

AC, axial chordoma; EAC, extra-axial chordoma; EMA, epithelial membrane antigen.
Bold values indicate $P < .05$.

data were classified into low- and high-expression groups for the subsequent analyses (Table 1). Fifty-three patients (74.6%) did not receive radiotherapy, whereas 18 patients (25.4%) were treated with radiotherapy, although the modality was not specified for most patients. The information on chemotherapy was rarely provided for the EAC cohort, and this variable was, therefore, not included in the subsequent analysis. The median LRFS and OS were 24.0 and 30.0 mo, respectively.

Patient and Tumor Characteristics of the AC Cohort

The AC cohort contained 75 patients from our institute. The patient clinicopathological features are detailed in Table 2. The results of the immunostaining for biomarkers in the AC subtype are illustrated in Figure 3, which showed no difference in expression patterns for most markers compared with the EAC data (Table 2). Nineteen patients (25.3%) received radiotherapy (including 10 treated by conventional photon irradiation and 9 treated with intensity modulated radiation therapy) vs 56 (74.7%) who did not. No patients received chemotherapy. The median LRFS and OS were 19.0 and 27.0 mo, respectively.

Comparison of Clinicopathological Characteristics Between EAC and AC Patients

The results of the comparisons of clinicopathological characteristics between patients with EAC and AC are shown in Table 2. Patients with EAC were significantly older than those with AC were. In contrast, EAC patients were more likely to have lobular growth patterns and higher expression levels of CAM5.2 than were patients with AC. Additionally, tumor recurrence and patient death were more commonly observed for AC than for EAC. There was also a significant difference in the extent of tumor invasion between EAC and AC cases, but this result could be

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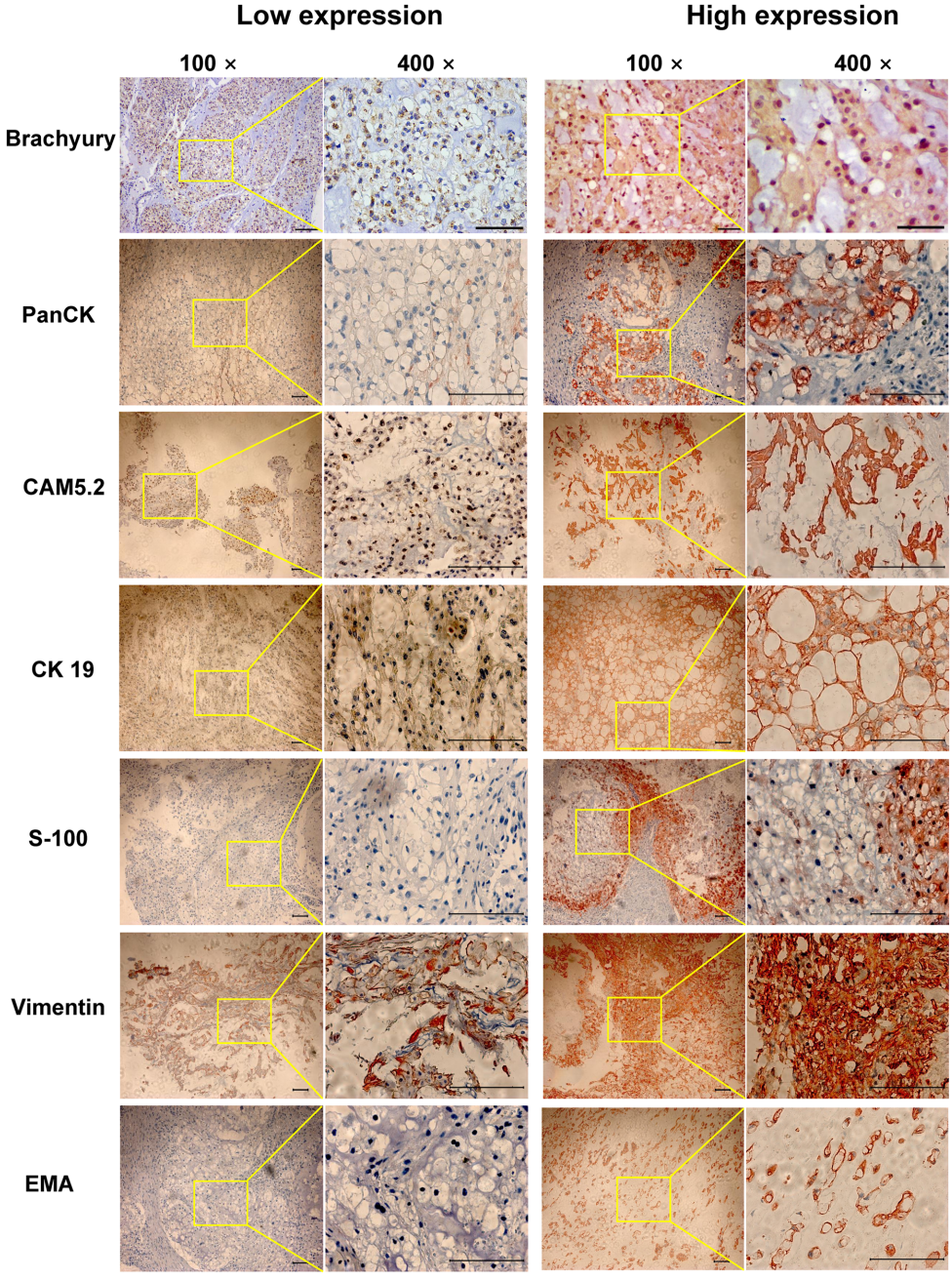


FIGURE 3. *Representative immunostaining images showing low- or high-expression levels for Brachyury, PanCK, CAM5.2, CK 19, S-100, vimentin, and EMA proteins in chordoma tissues. Scale bar = 100 μm. CK 19, cytokeratin 19; EMA, epithelial membrane antigen; PanCK, pancytokeratin.*

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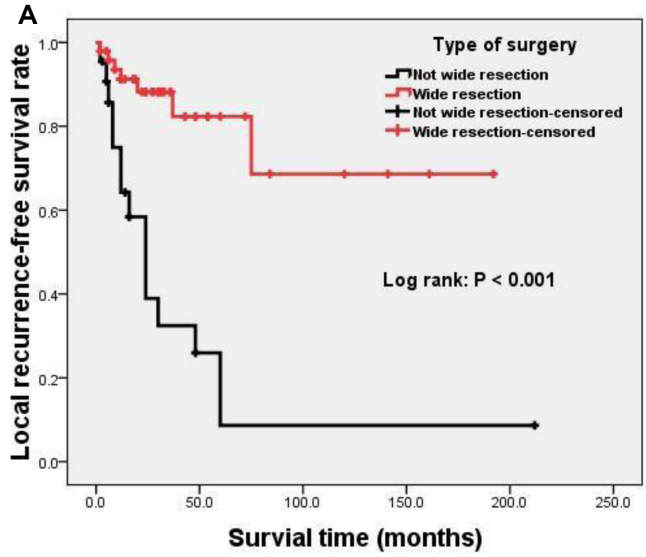


FIGURE 4. *Kaplan–Meier curves of the local recurrence-free survival of patients with EAC.* **A**, *Stratified by type of surgical resection (P < .001).* **B**, *Stratified by adjuvant radiotherapy (P = .021).*

caused by the bias that no cases with only soft tissue invasion were observed for AC.

Univariate Analyses of Prognostic Factors in EAC Patients

Wide resection of the tumors was significantly associated with favorable LRFS, whereas administration of adjuvant radiotherapy predicted poor outcome (Figure 4 and Table 3). In the univariate analysis for OS, we found that wide surgical resection and low vimentin expression correlated with better OS (Figures 5A and 5B and Table 3). Similarly, a strong association was also shown between the extent of tumor invasion and OS (Figure 5C and Table 3). Subgroup analysis found a significant difference in OS between patients with only intraosseous lesions and those with chordoma invading into the soft tissue and the bone ($P = .016$). There was also a trend toward better OS for patients having chordoma with only soft tissue invasion than the OS of those who had tumors infiltrating into the soft tissue and the bone, but the difference was not statistically significant ($P = .066$).

Multivariate Analysis of Prognostic Factors in EAC Patients

Cox multivariate analysis found that the type of surgical resection was the only independent prognostic factor of LRFS, whereas no parameters were predictive of OS (Figure 6).

Univariate Analyses of Prognostic Factors in AC Patients

In patients with AC, tumoral Brachyury expression, the duration of symptoms, and patient age were inversely associated with LRFS (Figures 7A–7C and Table 4). However, wide surgical resection and restricted extent of tumor invasion were related to prolonged survival (Figures 7D and 7E and Table 4). Furthermore, unlike in EAC, administration of adjuvant radiotherapy predicted favorable LRFS (Figure 7F and Table 4). Analyzing the OS, we found that low Brachyury expression on tumor cells and reduced duration of symptoms were correlated with better survival (Figures 8A and 8B and Table 4). A similar association was also observed between wide resection of the tumors and OS (Figure 8C and Table 4).

Multivariate Analysis of Prognostic Factors in AC Patients

Multivariate Cox regression analysis indicated that tumor Brachyury expression and the type of surgical resection were independent predictors of both LRFS and OS (Figure 9). In addition, this analysis also showed an independent association between postoperative adjuvant radiotherapy and LRFS, as well as between the duration of symptoms and OS (Figure 9).

DISCUSSION

Key Results

In this study, we performed an integrated analysis of the largest EAC cohort and investigated the association of clinicopathological parameters with patient survival. We also compared the differences in patient characteristics and prognostic patterns between EAC and AC patients. We found that EAC exhibited clinical characteristics similar to those of AC except for higher expression of CAM5.2, more common incidence of lobular growth pattern and better prognosis. Whereas wide surgical resection and confined invasion of tumors correlated with prolonged survival in both EAC and AC cohorts, most factors showed inconsistent association with survival between the 2

TABLE 3. Univariate Analyses of Prognostic Factors for LRFS and OS in Patients With EAC

Factors	Categories	LRFS				OS			
		n	Median Survival (mo)	$\chi 2$	*P* Value	*n*	Median Survival (mo)	$\chi 2$	*P* Value
Age (yr)	≤50	46	75	0.020	.886	44	–	2.427	.119
	>50	25	60			31	133		
Gender	Male	45	60	2.138	.144	50	133	2.742	.098
	Female	26	–			25	–		
Duration of symptoms (mo)[b]	Short (≤ cutoff)[a]	27	–	2.286	.131	17	–	1.156	.282
	Long (> cutoff)[a]	11	24			24	57		
Tumor size (largest diameter, cm)	≤5	25	–	0.074	.785	22	–	0.232	.630
	>5	22	75			26	–		
Tumor location	Upper respiratory tract	23	60	1.636	.651	22	133	1.160	.762
	Thorax	36	–			40	–		
	Limbs	9	75			10	–		
	Pelvic	3	12			3	14		
Extent of invasion	Soft tissue without bone invasion	34	75	2.348	.309	35	–	7.266	**.026**
	Soft tissue with bone invasion	19	48			22	57		
	intraosseous	17	–			17	–		
Type of surgery	Not wide resection	22	24	21.154	**<.001**	23	48	9.949	**.002**
	Wide resection	48	–			51	–		
Adjuvant radiotherapy	No	46	–	5.290	**.021**	45	–	2.684	.101
	Yes	14	37			17	–		
Lobular growth patterns	No	10	–	0.346	.556	11	–	0.096	.757
	Yes	37	60				–		
Pan-cytokeratin expression	Low	29	75	0.018	.894	31	–	0.315	.575
	High	12	–			12	–		
CAM5.2 expression	Low	14	–	1.088	.297	13	–	2.199	.138
	High	18	–			18	–		
Cytokeratin 19 expression	Low	20	–	0.081	.776	18	–	3.699	.054
	High	7	–			8	32		
S-100	Low	45	–	0.866	.352	48	–	0.569	.451
	High	8	24			7	–		
EMA expression	Low	23	–	1.678	.195	22	–	1.901	.168
	High	9	–			9	–		
Vimentin expression	Low	15	–	1.911	.167	16	–	4.852	**.028**
	High	9	–			9	32		
Brachyury expression	Low	23	75	1.945	.163	26	–	2.656	.103
	High	16	48			16	57		

EAC, extra-axial chordoma; EMA, epithelial membrane antigen; LRFS, local recurrence-free survival; OS, overall survival.
[a]Cutoff points for survival analysis of LRFS and OS were 13.0 and 10.5, respectively.
[b]*P* value from the log-rank test was corrected as previously suggested.[26]
Bold values indicate $P < .05$.

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groups. These data suggest that EAC likely has distinct molecular biology and clinical behavior from AC and may also provide useful information to better understand the prognostic characteristics as well as improve the risk classification of patients with EAC.

Influence of Surgical Resection Type on the Survival of EAC and AC Patients

Previous studies have widely suggested radical tumor resection as the most important factor in association with the long-term disease control of chordoma.[27,28] In line with this finding, our study showed that wide surgical resection of the tumors significantly influenced patient survival in both the EAC and AC cohorts. These data further highlight the importance of complete tumor removal in the clinical management of chordoma, which should be achieved when possible to prolong survival.[15] One major finding of this study was that EAC patients tended to experience better survival than did AC patients. As surgery type contributes largely to chordoma prognosis and EAC is anatomically easy to obtain complete surgical removal, some may attribute the different patient outcomes between EAC and AC to the different types of resection performed when treating these

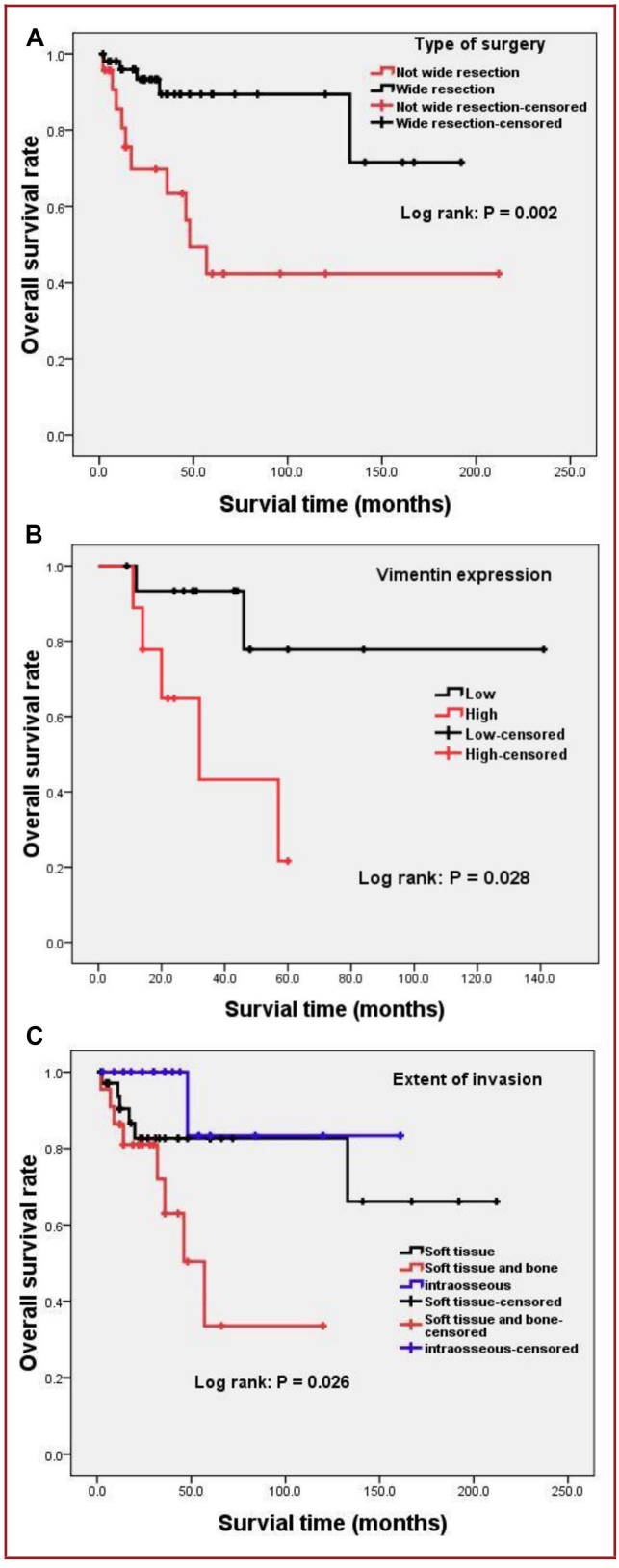


FIGURE 5. *Kaplan–Meier curves of the overall survival of patients with EAC.* **A**, *Stratified by type of surgical resection (P = .002).* **B**, *Stratified by vimentin expression (P = .028).* **C**, *Stratified by the extent of tumor invasion (P = .026).*

diseases. Contrary to this speculation, however, our analysis found no statistically significant difference in the type of surgery between the EAC and AC groups, implying that there are other factors responsible for the variation in survival.

Clinicopathological Similarities Between EAC and AC

In this study, we found that there were no differences in the expression patterns of most immunohistochemical markers (including Brachyury, pancytokeratin, cytokeratin 19, EMA, and S-100) between EAC and AC lesions. Similarly, most clinical features did not differ significantly between these pathologies. Together, these outcomes indicate that EAC shares certain similarities with the axial type.

Differences in Immunohistopathological and Prognostic Features Between EAC and AC

In the current study, we found that Brachyury expression was a significant predictor of clinical outcome in patients with AC. This result is in agreement with published data showing the critical role of Brachyury protein in chordoma growth and progression.[29-32] However, we did not detect any correlation between Brachyury expression and the outcome of EAC patients. Similar phenomena were also observed for tumor vimentin expression and the duration of symptoms, which both showed differential prognostic implications in the EAC and AC groups. In addition, our analysis also revealed a significant or borderline significant difference in terms of lobular growth pattern and tumoral CAM5.2 or vimentin expression between EAC and AC. These findings collectively suggest that EAC may have disease origin at least partly different from that of AC, thus leading to distinct biological behavior and characteristics in disease progression. Further molecular studies may help uncover the mechanisms underlying EAC development and open up new therapeutic approaches for this rare pathology.

Prognostic Role of Cytokeratin, EMA, and S-100 Expression in Chordoma

Noticeably, we investigated for the first time the prognostic value of cytokeratin, EMA, and S-100 expression in chordoma. Published data mostly discuss their diagnostic roles in chordoma, and no studies have attempted to evaluate their impacts on prognosis.[16,18,33-35] Here, we found a lack of predictive impact of these immunohistochemical biomarkers, which contradicts previous reports showing their significant value for outcome prediction in cancer patients.[36-41] This inconsistency may be caused by the different cancer types studied or the small sample size included in our analysis, thus leading to a low statistical power. Future studies with a large number of patients are

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FIGURE 6. *Multivariate Cox regression model for prognostic factors in patients with EAC. The red boxes indicate the hazard ratio, and the horizontal lines represent 95% confidence intervals.*

required to determine the exact role of these markers in chordoma prognosis.

Impact of the Extent of Tumor Invasion on Chordoma Outcome and Its Potential Molecular Basis

It has been widely reported that the presence of tumor invasion into the surrounding tissues is associated with an increased risk of disease recurrence and progression in chordoma.[12,15,42] Consistent with this finding, our study revealed a significant relationship between the extent of tumor invasion and patient survival in both chordoma cohorts. It is reasonable to infer that the worse outcome for chordoma with extensive invasion may be due to the high probability of residual tumor left after surgical excision. Another possible explanation for such an association is that chordoma lesions with invasion into surrounding structures are more likely to have histological vascular involvement and microskip metastasis, which both have been recently demonstrated as important factors predicting recurrence and survival in spinal chordoma patients.[43] In addition, we consider the molecular basis as the main determinant

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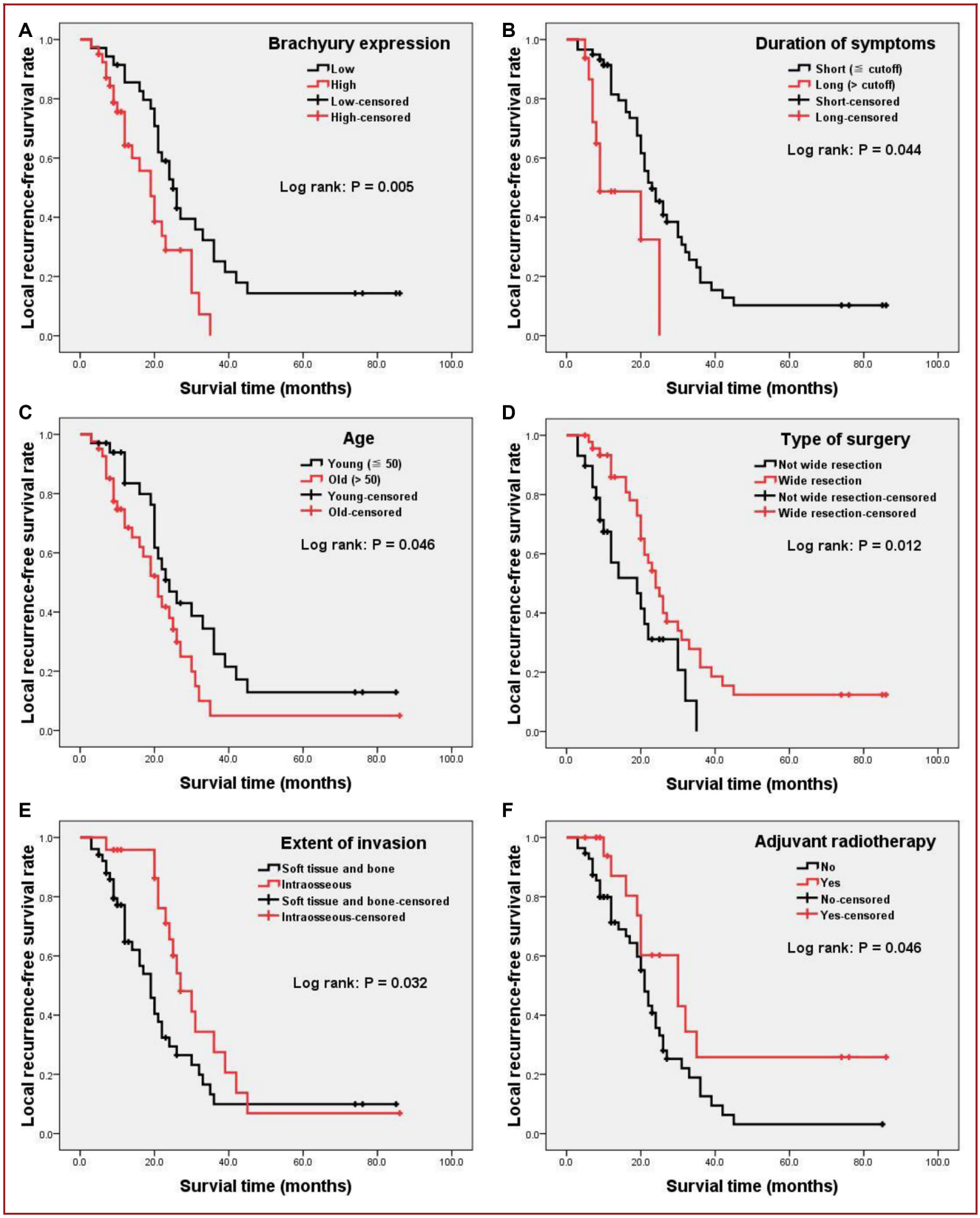


FIGURE 7. *Kaplan–Meier curves of the local recurrence-free survival of patients with AC.* **A**, *Stratified by Brachyury expression (P = .005).* **B**, *Stratified by duration of symptoms (P = .044).* **C**, *Stratified by patient age (P = .046).* **D**, *Stratified by type of surgery (P = .012).* **E**, *Stratified by the extent of tumor invasion (P = .032).* **F**, *Stratified by adjuvant radiotherapy (P = .046).*

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TABLE 4. Univariate Analyses of Prognostic Factors for LRFS and OS in Patients With AC

Factors	Categories	LRFS				OS			
		n	Median survival (mo)	χ^2	*P* Value	*n*	Median survival (mo)	χ^2	*P* Value
Age (yr)	≤50	34	24	3.993	**.046**	34	97	2.429	.119
	>50	41	21			41	35		
Gender	Male	49	20	1.692	.193	49	56	1.053	.305
	Female	26	31			26	97		
Duration of symptoms (mo)[b]	Short (≤cutoff)[a]	59	23	9.492	**.044**	59	84	13.069	**<.001**
	Long (>cutoff)[a]	16	9			16	23		
Tumor size (largest diameter, cm)	≤5	36	24	1.965	.161	36	84	0.425	.515
	>5	39	21			39	57		
Tumor location	Spine	62	21	3.721	.054	62	56	1.068	.301
	Skull base	13	30			13	84		
Extent of invasion	Soft tissue with bone invasion	51	19	4.584	**.032**	51	57	1.781	.182
	Intraosseous	24	27			24	97		
Type of surgery	Not wide resection	29	19	6.301	**.012**	29	33	7.291	**.007**
	Wide resection	46	24			46	97		
Adjuvant radiotherapy	No	56	21	3.989	**.046**	56	48	0.291	.590
	Yes	19	30			19	84		
Lobular growth patterns	No	47	21	0.002	.965	47	73	0.304	.581
	Yes	28	24			28	48		
Pan-cytokeratin expression	Low	58	23	0.190	.663	58	73	0.000	.989
	High	17	20			17	—		
CAM5.2 expression	Low	59	21	0.169	.681	59	73	1.640	.200
	High	16	24			16	—		
Cytokeratin 19 expression	Low	60	24	0.397	.529	60	73	0.366	.545
	High	15	12			15	84		
S-100	Low	60	22	0.056	.814	60	73	0.602	.438
	High	15	30			15	48		
EMA expression	Low	60	22	0.021	.884	60	73	0.001	.977
	High	15	20			15	56		
Vimentin expression	Low	61	22	0.930	.335	61	57	1.820	.177
	High	14	31			14	—		
Brachyury expression	Low	35	25	7.852	**.005**	35	128	13.511	**<.001**
	High	40	19			40	28		

AC, axial chordoma; EMA, epithelial membrane antigen; LRFS, local recurrence-free survival; OS, overall survival.
[a]Cutoff point for survival analysis of both LRFS and OS was 36.5.
[b]*P* value from the log-rank test was corrected as previously suggested.[26]
Bold values indicate $P < .05$.

implicated in the promotion of chordoma invasiveness. Published data have revealed differential protein expression profiles between endophytic and exophytic types of clival chordoma.[44] Furthermore, epigenetic dysregulation and aberrant expression of several proteins have also been correlated with chordoma invasion and prognosis.[20-22,45-47] Additionally, a high density of microenvironmental PD-1-positive lymphocytes was linked with increased invasion of the surrounding muscle tissue by chordoma cells.[24] Above all, these results indicate that a complex molecular mechanism, together with the immune microenvironment, may contribute to chordoma infiltration into the surrounding tissues, thus leading to poor patient outcome.

Differential Prognostic Implications of Radiotherapy between EAC and AC

Interestingly, our study found that radiotherapy exerted a negative effect on survival in patients with EAC, whereas it conferred benefit on prognosis in AC, as previously reported.[15,48]

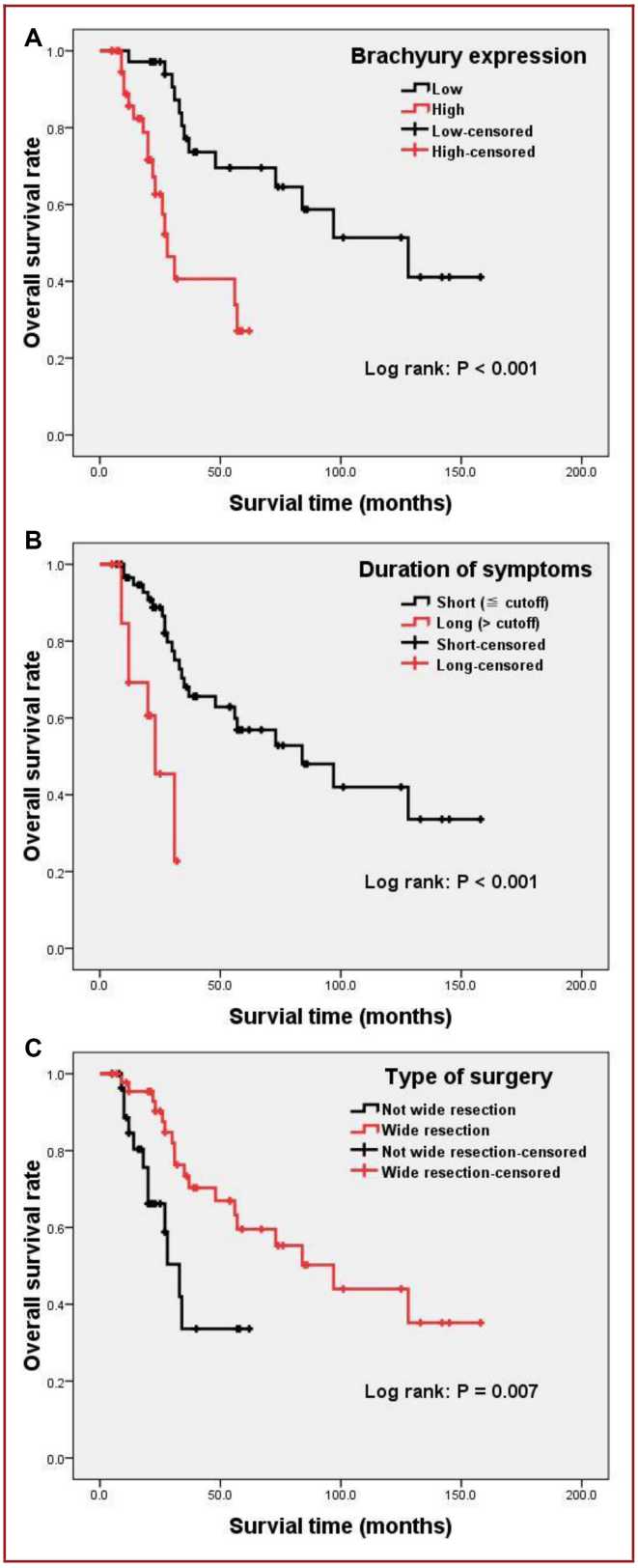


FIGURE 8. *Kaplan–Meier curves of the overall survival of patients with AC.* **A**, *Stratified by Brachyury expression (P < .001).* **B**, *Stratified by duration of symptoms (P < .001).* **C**, *Stratified by type of surgery (P = .007).*

These findings further suggest different molecular characteristics among EAC and AC subpopulations and may also represent a selection bias that radiotherapy has a tendency to be assigned for patients with inoperable or more extensive disease.[49-51] Furthermore, the modality of radiation therapy was not specified in most of the included studies, which may also lead to a distorted interpretation of the actual effect of radiotherapy on survival. Additionally, radiation can promote epithelial–mesenchymal transition and induce the generation of new cancer stem cells from nonstem cancer cells in various human cancers.[52,53] These findings may provide a novel insight into the poor outcome for EAC patients who received radiotherapy. Further comparative proteomics studies with the detection of newly generated cancer stem cells after treatment with radiation in EAC and AC tissues may be helpful in determining the precise mechanisms of the different prognostic patterns between these chordoma variants.

Limitations

Unlike previous reports,[19] we failed to define a significant association between lobular growth pattern and chordoma prognosis. This discrepancy may arise because of different chordoma types and different patient characteristics included in the statistical analysis. Additionally, it should be noted that our study is limited by the potential heterogeneity of data reporting on the immunohistochemical expression of several biomarkers examined. As most studies provided no detailed information on the specific criteria for immunohistochemical evaluation, we simply separated the data into high- and low-expression groups in attempt to reduce the heterogeneity and make statistical analysis possible.

CONCLUSION

This study provided a summary of clinicopathological features and prognostic factors in a large cohort of EAC patients. EAC had similar characteristics to its axial counterpart, except for having high CAM5.2 expression, common lobular growth pattern, and better prognosis. Although the type of surgery and the extent of tumor invasion showed consistent prognostic implications in both the EAC and AC groups, these 2 chordoma subtypes predominantly exhibited different prognostic patterns. These data suggest potentially distinct biological behaviors between EAC and AC and may also be useful in improving prognostic risk stratification and guiding therapeutic optimization for EAC patients.

Disclosures

Dr Wang receives research grants from the Natural Science Foundation of Hunan Province (Grant No. 2018JJ3738). Dr Zou is supported by the China Scholarship Council (No. 201706370070). The other authors have no personal,

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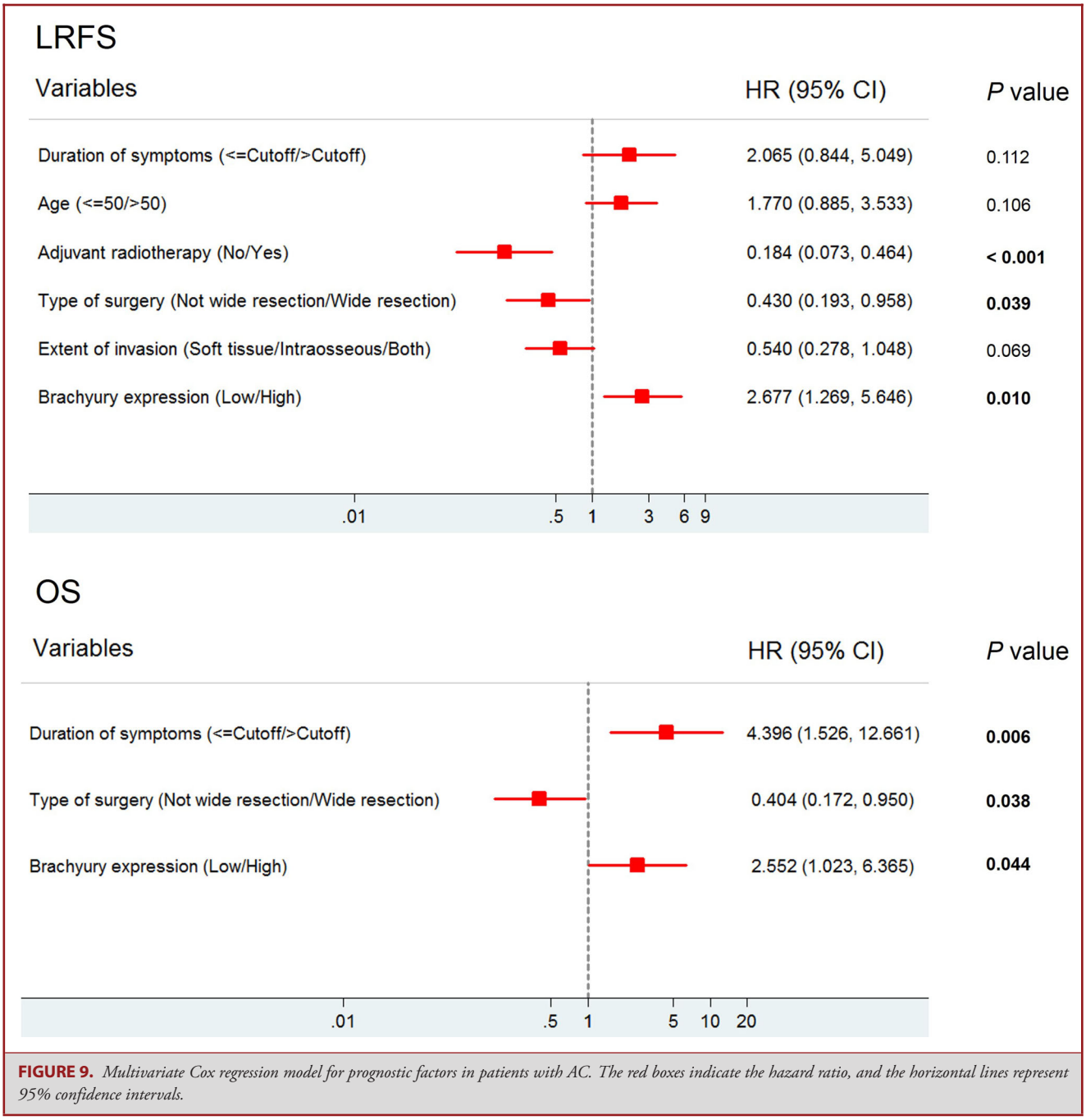


FIGURE 9. *Multivariate Cox regression model for prognostic factors in patients with AC. The red boxes indicate the hazard ratio, and the horizontal lines represent 95% confidence intervals.*

financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content 1. Table. Detailed information on the antibodies used for the immunohistochemical assays.

Supplemental Digital Content 2. Figure. Determination of the cutoff value for duration of symptoms in the prognosis analysis.

Supplemental Digital Content 3. Table. Characteristics of the included studies.

Supplemental Digital Content 4. Uncited References. List of the included studies addressing EAC patients in the literature.

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EQ-5D Quality-of-Life Analysis and Cost-Effectiveness After Skull Base Meningioma Resection

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Received, June 25, 2018.
Accepted, January 28, 2019.
Published Online, March 14, 2019.

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BACKGROUND: Skull base meningioma management is complicated by their proximity to intracranial neurovascular structures because complete resection may pose a risk of worsening morbidity.

OBJECTIVE: To assess the influence of clinical outcomes and surgical management on patient-perceived quality-of-life outcomes, value, and cost-effectiveness.

METHODS: Patients who underwent resection of a skull base meningioma, had adequate clinical follow-up, and completed EQ-5D-3L questionnaires preoperatively and at 1 mo and 1 yr postoperatively were identified in a retrospective review. Cost data from the Value Driven Outcomes database were analyzed.

RESULTS: A total of 52 patients (83.0% women, mean age 51.9 yr) were categorized by worsened (n = 7), unchanged (n = 24), or improved (n = 21) EQ-5D-3L index scores at 1-mo follow-up. No difference in subcategory cost contribution or total cost was seen in the 3 groups. Patients with improved scores showed a steady improvement through each follow-up period, whereas those with unchanged or worsened scores did not. Mean quality-adjusted life years (QALYs) and cost per QALY improved for all groups but at a higher rate for patients with better outcomes at 30-d follow-up. Female sex, absence of proptosis, nonfrontotemporal approaches, no optic nerve decompression, and absence of surgical complications demonstrated improved EQ-5D-3L scores at 1-yr follow-up. A mean cost per QALY of $27 731.06 ± 22 050.58 was observed for the whole group and did not significantly differ among patient groups ($P = .1$)

CONCLUSION: Patients undergoing resection of skull base meningiomas and who experience an immediate improvement in EQ-5D are likely to show continued improvement at 1 yr, with improved QALY and reduced cost per QALY.

KEY WORDS: Cost-effectiveness, EQ-5D, Meningioma, Outcomes, Quality of life, Quality-adjusted life years, Skull base, Value

Neurosurgery 85:E543–E552, 2019 DOI:10.1093/neuros/nyz040 www.neurosurgery-online.com

Intracranial meningiomas are the most commonly diagnosed primary brain tumors in the US.[1] Most meningiomas follow a benign clinical course and are treated with conservative management.[2] For symptomatic meningiomas, treatment is with resection or radiation.[2,3] Skull base meningioma resection presents a unique challenge because of the proximity of vital neurovascular structures to tumor locations.[4,5] Gross-total resection of skull base meningiomas is associated with the lowest rate of local recurrence; however, complete resection of skull base meningiomas can result in significant morbidity, including hemorrhage, cerebrospinal fluid leak, cerebral vascular accident, infection, and worsening neurological function.[4,6,7]

Several neurosurgical studies have evaluated how to improve the patient-perceived quality of life (QOL), but how objective postoperative clinical findings and surgical techniques are associated with subjective QOL measures

ABBREVIATIONS: ASA, American Society of Anesthesiologists; **CER,** cost-effectiveness ratio; **ICER,** incremental cost-effectiveness ratio; **MCID,** minimum clinically important difference; **QALY,** quality-adjusted life year; **QOL,** quality of life; **WHO,** World Health Organization

remains largely unknown,[6,8,9] particularly in patients with skull base tumors, who are at inherently higher risk of neurovascular injury. One measure of QOL, the EQ-5D-3L index score, has been shown to demonstrate meaningful changes as clinical status changes for various patient diseases.[10-13] We analyzed patient-reported EQ-5D-3L scores of patients with skull base meningiomas to understand how surgical interventions, clinical outcomes, and complications affect patient-reported QOL and how QOL is associated with treatment cost.

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METHODS

Patients

After receiving the institutional review board approval with a waiver of informed consent, we performed a retrospective chart review of adult patients (> 18yr) who underwent skull base meningioma resection at a single institution from August 2012 to July 2016. All patients undergoing routine cranial surgery at our institution are provided with EQ-5D-3L questionnaires (https://euroqol.org/; EuroQol, Rotterdam, The Netherlands), but the completion of the questionnaires is not required. Patients were included in the study if they completed preoperative and 1-mo postoperative (ie, follow-up #1) questionnaires. Subsequent patient questionnaires at 1-yr postoperative or beyond (ie, follow-ups #2 and #3) were not completed by all patients.

A manual chart review compiled relevant data from electronic health records. Patient demographics included age, sex, race, body mass index, diagnosis of meningiomatosis, neurofibromatosis type 1 and 2, smoking status, insurance type, and disposition. Tumor location and size were determined by the assessment of magnetic resonance images. Presenting and postsurgical clinical symptoms were identified from neurological examination notes and patient histories. Tumor characteristics included grade, location, size, resection approach, cranial nerve involvement, and whether the meningioma was a recurrence. Simpson grade I–III resections involved gross-total resection with complete removal of tumor and total or partial dural coagulation. Simpson grade IV and V resections involved near-total or subtotal resections, with obvious residual tumor and incomplete dural resection or coagulation. The pathological record confirmed meningioma diagnosis and the World Health Organization (WHO) grade. Surgical characteristics included the American Society of Anesthesiologists (ASA) grade, surgical approaches, and complications.

Quality-of-Life Measures

EQ-5D-3L questionnaires from preoperative clinical visits and subsequent follow-ups were scored after the approval for research use. The questionnaire is a standardized tool used to measure patient-reported health outcomes in 5 separate categories (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[14] The patient-reported outcomes are converted into an EQ-5D-3L index score, which converts individual patient answers into a global index score that depends on the specific geographic population. Scores range from 1, representing the best health possible, to 0, representing death. EQ-5D-3L index scores were converted into quality-adjusted life years (QALYs) by multiplying the index score and time from the preoperative visit with the specific follow-up visit (eg, 1 QALY = 1 year of life × 1 utility value). Patients were divided into 3 groups depending on whether their EQ-5D-3L scores were improved, unchanged, or worsened at 30-d follow-up.

Care Costs

Costs of delivering care were obtained from the Value Driven Outcomes system, which derives true costs to the healthcare system, not charges or reimbursements.[12,15-18] Costs are calculated from purchase prices of instruments and pharmaceuticals, time for treatment in individual units, or radiological studies, etc. Total costs were analyzed and subcategory costs for facility, pharmacy, laboratory, supplies and implants, and imaging were calculated. Because actual dollar amounts cannot be reported as per the institutional data agreement, the subcategory cost is reported as a percentage of total cost. Costs are totaled for the entire cohort, and each patient's fraction of total cost contribution is calculated to allow comparisons. The mean percentage of total cost may not necessarily total 100%. To determine the subgroup cost contribution, the subgroup cost for each patient was divided by the total, and percentages will equal 100%. The cost-effectiveness ratio (CER), ie, cost per QALY, can be derived by dividing the total dollar cost by QALYs at specific time points. An incremental cost-effectiveness ratio (ICER) could not be calculated because no control group (observation or radiosurgery) was available.

Statistical Analysis

Continuous variables are reported as means with standard deviations and were analyzed by *t*-test. Certain means that are reported as standard error of the mean are noted. Noncontinuous variables were analyzed using the chi-squared test. Multiple groups of continuous variables were evaluated by one-way analysis of variance (ANOVA) with Tukey post-hoc comparisons. SPSS (version 22.0, IBM Corp, Armonk, New York) was used for statistical analysis, with $P < .05$ considered significant. The STROBE guidelines were used during the preparation of this paper.

RESULTS

Patient Characteristics

A total of 52 adult patients (mean age 51.9 ± 11.9 yr, 83% female) were included (Table 1). The most frequent presenting symptoms were vision change (61.5%), headache (36.5%), other new cranial nerve deficit (30.8%), ambulation deficits (26.9%), proptosis (25.0%), and tinnitus (23.1%). Meningiomas were mostly WHO grade I (92.3%), but some were WHO grade II (7.7%). Of the sample, 3.8% of patients had undergone previous radiation treatment for cancer unrelated to their meningioma resection, 13.5% were presenting for recurrent disease, and 59.6% had at least 1 other medical comorbidity.

Surgical Characteristics

Surgical characteristics are presented in Table 2. Most patients had mild (ASA Grade 2, 51.9%) or severe (grade 3, 38.5%) systemic disease; very few were healthy (grade 1, 3.8%) or incapacitated (grade 4, 1.9%) at the time of surgery. Tumors in the series were most commonly found in the tuberculum sellae (19.2%), petroclival region (15.4%), and sphenoid wing (15.4%).

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TABLE 1. Characteristics of 52 Patients Treated with Resection of Skull Base Meningioma

Patient Characteristics	Value
Age, yr (mean ± STD)	51.9 ± 11.9
Sex, female	43 (83%)
Body mass index, kg/m^2 (mean ± STD)	29.4 ± 5.7
Race	
Caucasian	44 (84.6%)
Black/African American	1 (1.9%)
Asian/Pacific Islander	1 (1.9%)
Other	5 (9.6%)
Unknown	1 (1.9%)
Tobacco use	14 (26.9%)
Alcohol use	23 (44.2%)
Mutational status	
NF1	0 (0.0%)
NF2	1 (1.9%)
Meningiomatosis	1 (1.9%)
WHO grade meningioma	
Grade I	48 (92.3%)
Grade II	4 (7.7%)
Prior radiation for unrelated cancer	2 (3.8%)
Recurrence	7 (13.5%)
Medical comorbidities	31 (59.6%)
Preoperative symptoms	
Vision change	32 (61.5%)
Headache	19 (36.5%)
New cranial nerve deficit	16 (30.8%)
Ambulation difficulties	14 (26.9%)
Proptosis	13 (25.0%)
Tinnitus	12 (23.1%)
Cognitive decline	5 (9.6%)
Seizure	3 (5.8%)
Vertigo	3 (5.8%)
Incidental tumors	3 (5.8%)
Hydrocephalus	3 (5.8%)
Insurance type	
Private	25 (48.1%)
Public (Medicare/Medicaid)	11 (21.2%)
None	1 (1.9%)
Unknown	15 (28.8%)

Value indicates number (% of total) unless otherwise indicated.

TABLE 2. Surgical Characteristics of 52 Patients Treated with Resection of Skull Base Meningioma

Patient characteristics	Value
American Society of Anesthesiologist Scale	
Healthy	2 (3.8%)
Mild systemic disease	27 (51.9%)
Severe systemic disease	20 (38.5%)
Incapacitating disease	1 (1.9%)
Unknown	2 (3.8%)
Tumor location	
Tuberculum sellae	10 (19.2%)
Petroclival	8 (15.4%)
Sphenoid wing	8 (15.4%)
Cavernous sinus	5 (9.6%)
Posterior fossa	5 (9.6%)
Sphenoorbital	5 (9.6%)
Convexity/skull base	3 (5.8%)
Clinoidal	2 (3.8%)
Cerebellopontine angle	1 (1.9%)
Lateral medullary	1 (1.9%)
Olfactory groove	1 (1.9%)
Pineal	1 (1.9%)
Suprasellar	1 (1.9%)
Unknown	1 (1.9%)
Tumor volume, cm^3 (mean ± STD)	14.0 ± 23.8
Surgical approach	
Frontotemporal	37 (71.2%)
Retrosigmoid	5 (9.6%)
Suboccipital	3 (5.8%)
Bifrontal	1 (1.9%)
Far lateral	1 (1.9%)
Occipital	1 (1.9%)
Parietal	1 (1.9%)
Retrosigmoid and frontotemporal	1 (1.9%)
Transnasal	1 (1.9%)
Transpetrosal and middle fossa	1 (1.9%)

Value indicates number (% of total) unless otherwise indicated.

Mean tumor volume was 14.0 ± 23.8 cm^3. The frontotemporal surgical approach was used most often (71.2%).

Patient Outcomes

Patient–hospital outcomes are shown in Table 3. The average length of stay was 5.1 ± 2.1 d. Simpson grade I-III resection was achieved in 53.8% (n = 28) of patients, whereas Simpson grade IV and V resection was seen in 46.2% (n = 24) of patients. Patients often discharged home (78.0%). Transient postoperative issues were new or worsening cranial nerve deficits (52.3%), anemia requiring transfusion (5.8%), aphasia (3.8%), and seizure (1.9%). Surgical complications involved CSF leak (7.7%), unexpected cranial nerve injury (1.9%), and infection requiring surgical treatment (1.9%). Medical complications included delayed cerebrovascular accident (1.9%), and urinary tract infection (1.9%).

EQ-5D Scores and Subgroup Analysis

The average (±SEM) preoperative EQ-5D-3L index scores (Table 3) of all included patients were 0.78 ± 0.20. The mean preoperative EQ-5D-3L index scores were 0.93 ± 0.04, 0.83 ± 0.03, and 0.67 ± 0.05 for patients with worsened, unchanged, or improved scores, respectively. The mean overall length of follow-up was 9.1 ± 7.9 mo: first follow-up was at 1.2 ± 0.02 mo and second follow-up (n = 39 patients) was at 11.1 ± 10.8 mo. The mean EQ-5D-3L index scores were 0.69 ± 0.07, 0.75 ± 0.04, and 0.8 ± 0.04 at follow-up #1 and 0.75 ± 0.09, 0.81 ± 0.05, and 0.9 ± 0.04 at follow-up #2

TABLE 3. Patient Outcomes of 52 Patients Treated with Resection of Skull Base Meningioma

Patient characteristics	Value
Length of stay, d (mean ± STD)	5.1 ± 2.1
Extent of resection	
Simpson grades I-III	28 (53.8%)
Simpson grades IV-V	24 (46.2%)
EQ-5D-3L index score change	
Worsened at 30 d	21 (40.4%)
Unchanged at 30 d	24 (46.2%)
Improved at 30 d	7 (13.5%)
Discharge disposition (% total)	
Home	41 (78.0%)
Home health	2 (3.8%)
Acute rehab	7 (13.5%)
Other	2 (3.8%)
Follow-up, months (mean ± STD)	
Overall follow-up	9.1 ± 7.9
Follow-up #1 (~30 d)	1.2 ± 0.02
Follow-up #2 (~1 yr)	11.1 ± 10.8
Follow-up #3 (other)	8.9 ± 2.5
Postoperative symptoms (% total)	
New or worsening cranial nerve deficit	22 (52.3%)
Anemia requiring transfusion	3 (5.8%)
Transient aphasia	2 (3.8%)
Seizure	1 (1.9%)
Surgical complications (% total)	
Cerebrospinal fluid leak	4 (7.7%)
Unexpected cranial nerve injury	1 (1.9%)
Infection requiring surgery	1 (1.9%)
Medical complications (% total)	
Cerebrovascular accident	1 (1.9%)
Urinary tract infection	1 (1.9%)

for patients that worsened, remained unchanged, or improved, respectively. Only 6 patients had later follow-ups (eg, follow-up #3). There was no significant difference between preoperative and follow-up EQ-5D-3L scores at either time point for all meningioma patients as a group.

Patients with improved scores on follow-up showed the best recovery of self-care subscores (eg, washing/dressing) compared with changes in mobility, usual activities, and pain/discomfort. Anxiety/depression in these patients worsened despite overall improvements in EQ-5D-3L scores. Neither age nor recurrence resulted in significant differences between preoperative and follow-up EQ-5D-3L scores (Figure 1). Female patients had a significant score improvement at the second follow-up ($P < .05$, t-test), but there were no other sex-associated differences in scores. No differences in EQ-5D-3L scores were specifically observed for patients with vision changes, headaches, ambulation deficits, tinnitus, or new cranial nerve deficits (Figure 2). Patients with no proptosis, nonfrontotemporal approaches, or no optic nerve decompression showed improved EQ-5D-3L scores at the second follow-up ($P < .05$, t-test, Figures 2 and 3) as did those who had no surgical complications ($P < .05$, t-test, Figures 2 and 3).

Patient Costs

Cost distribution of facility, pharmacy, supplies/implants, imaging, and laboratory costs did not differ significantly depending on the patient-perceived outcome score group (Figure 4A-4C). Facility costs accounted for the highest percentage of costs followed by supplies/implants for all groups. The mean percentage of total cost was used to compare costs across patient outcome groups to evaluate which group had the most expensive care (Figure 4D). The mean percentage of total costs per patient with worsened, unchanged, or improved EQ-5D-3L scores were 2.4 ± 0.8%, 1.9 ± 0.6%, and 2.0 ± 0.7%, respectively ($P = .2$, one-way ANOVA).

Cost-Effectiveness Analysis

Perhaps unsurprisingly, patients with improved EQ-5D-3L scores started at a significantly lower score preoperatively compared with patients with unchanged or worsened scores ($P < .002$, one-way ANOVA; Figure 5A). Patients with improved scores at 1-mo follow-up continued to show improvement at 1 yr and beyond, whereas other patients remained stable, suggesting a possibility of predicting long-term outcome. Patients with worsened, unchanged, and improved self-perceived outcomes showed an average change of 0.18 ± 0.18, 0.01 ± 0.06, and 0.22 ± 0.19 in EQ-5D-3L index scores between the preoperative and final follow-up, respectively. There was no difference among the score categories in EQ-5D-3L index scores at follow-up #1 ($P = .4$, one-way ANOVA), follow-up #2 ($P = .2$), or follow-up #3 ($P = .97$). However, QALYs were also calculated because they factor in specific patient follow-up time points in their calculation. Patients with improved outcome at follow-up #1 had significantly better QALYs at follow-up #2 ($P = .04$, one-way ANOVA, Figure 5B). The cost per QALY decreased for all patients during follow-up and did not significantly differ for groups at follow-up #1 ($P = .3$), follow-up #2 ($P = .1$), or follow-up #3 ($P = .4$) (one-way ANOVA, Figure 5C). An overall cost per QALY of $27 731.06 ± 22 050.58 (median $21 938.18; range $4834.22–105 610.67) was observed. A total of 6 patients (scattered among all outcome groups) showed cost per QALY of > $50 000. Analysis of cost per QALY at 1 yr for specific outcomes was performed (Table 4). Expectedly, patients with improved outcome ($21 958 ± 15 544 vs $59 983 ± 85 493, $P = .05$) and shorter length of stay ($25 406 ± 26 587 vs $75 800 ± 100 688, $P = .03$) showed a lower cost per QALY. No change in cost per QALY was seen for surgical complications ($P = .6$), medical complications ($P = .7$), extent of resection ($P = .9$), and disposition ($P = .09$), although results were limited by subgroup sample size.

DISCUSSION

Management of skull base meningiomas presents a significant challenge because of the close proximity of neurovascular structures and difficulty in surgical approaches.[4,19] This

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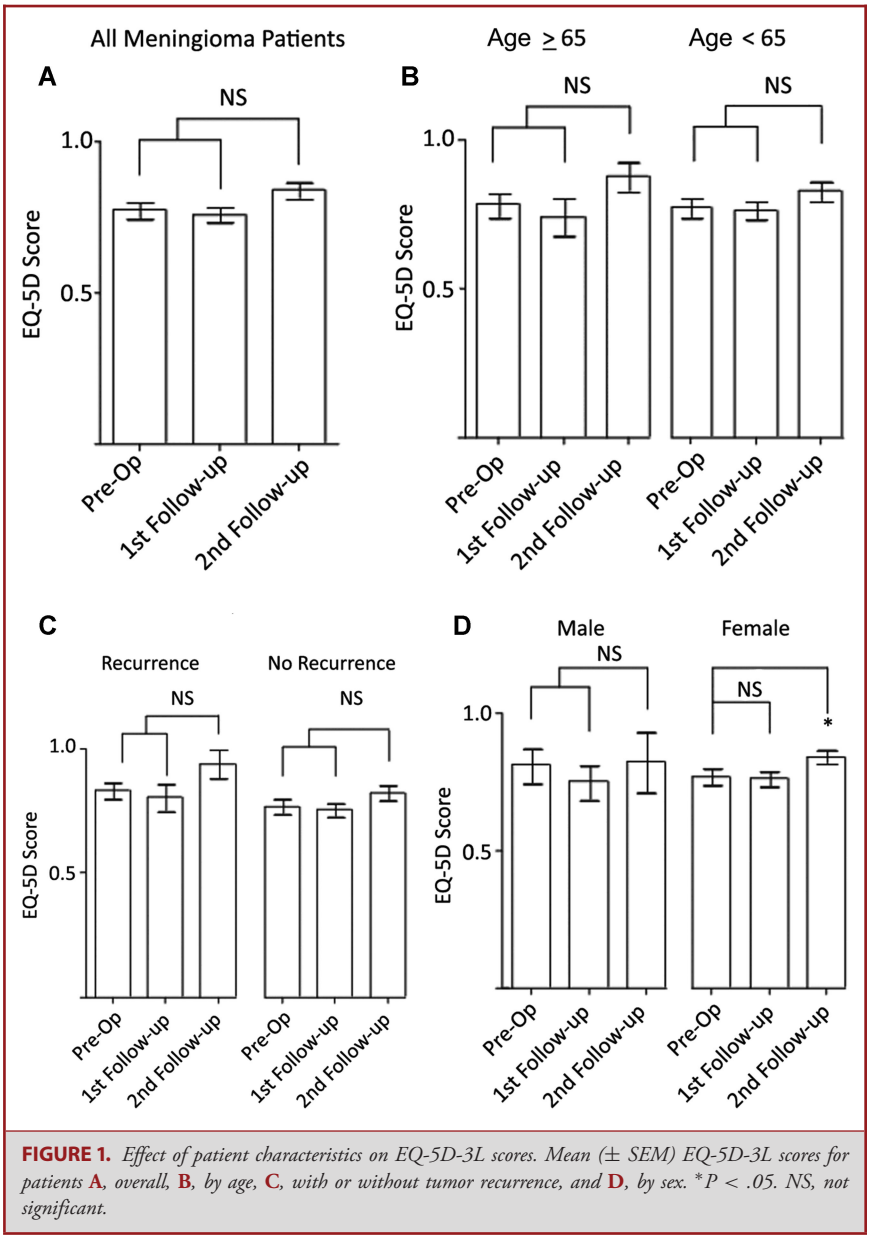


FIGURE 1. *Effect of patient characteristics on EQ-5D-3L scores. Mean (± SEM) EQ-5D-3L scores for patients* **A**, *overall,* **B**, *by age,* **C**, *with or without tumor recurrence, and* **D**, *by sex.* $^{*}P < .05$. *NS, not significant.*

study evaluates the effect on QOL and the value for resection among patients with skull base meningiomas. The results of this study demonstrated that many patients who underwent resection of skull base meningiomas showed improvement in EQ-5D-3L measures (40.4%) at 1 yr postoperatively, but a similar number remained stable (46.2%), and approximately a sixth had worse EQ-5D-3L scores (13.5%). More importantly, those who had improvement at 1-mo follow-up continued to report improvement over time. These results suggest that early improvement in QOL measures can predict sustained improvement at 1-yr follow-up. Patients that improved showed an average increase of 0.22 in EQ-5D-3L scores, approaching the minimum clinically important difference (MCID) for neurosurgical patients, although the MCID remains controversial for brain tumor patients.[20,21] Patients with lower initial EQ-5D-3L scores showed the greatest improvement at 1 yr, suggesting that tumors that cause disability and reduce the ability to perform activities of daily living might be good candidates for surgical treatment. Although not all patients showed improved outcomes, those with stable outcomes are still notable because the goals of surgery can include decompression of optic nerves, prevention of future tumor growth, and separation of normal

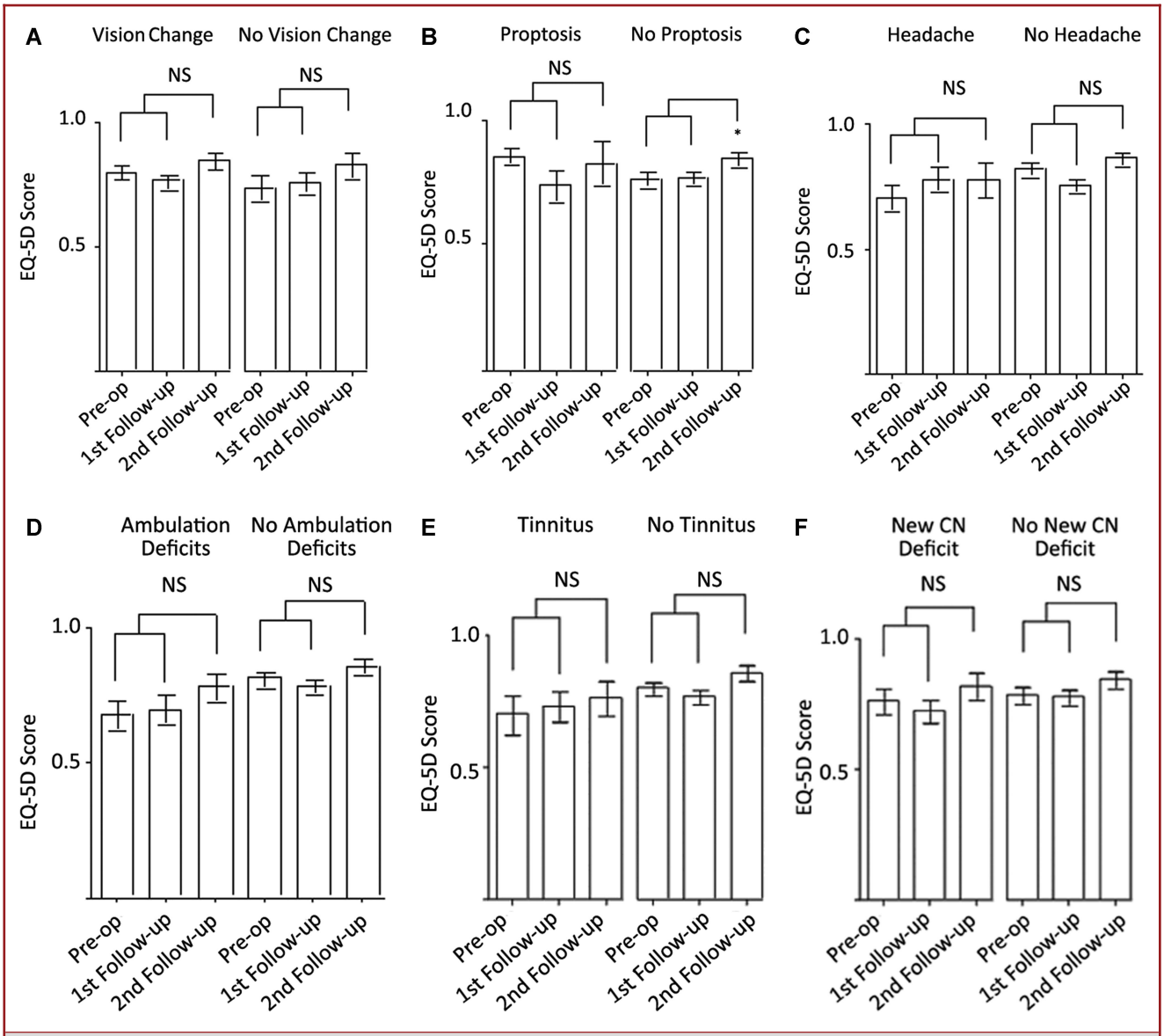


FIGURE 2. *Effect of patient symptoms on EQ-5D-3L index score during the follow-up period. Mean (± SEM) EQ-5D-3L scores for patients with* **A**, *vision change,* **B**, *proptosis,* **C**, *headaches,* **D**, *ambulation deficits,* **E**, *tinnitus, or* **F**, *new cranial nerve deficits. *P < .05. NS, not significant.*

neurovascular structures to allow future radiosurgical treatment. Preservation of function and QOL, in the setting of disease that is likely to compromise neurological function, can carry value.

Identification of patient factors that predict outcome remained limited. Patients who were female, had no proptosis, showed no surgical complications, underwent nonfrontotemporal approaches, or underwent no optic nerve decompression had improved EQ-5D-3L scores on late follow-up. Patients with improved scores showed better recovery of self-care subscores. Although the better QOLs seen in the absence of surgical complications make sense, other clinical subgroups require additional research to better understand this observation. It is possible that vision plays the key role in affecting the QOL. Patients without proptosis or a need for optic nerve decompression seemed to fare better. In addition, patients with nonfrontotemporal decompression, which is commonly used at our institution to decompress optic nerves affected by sphenoid wing or sphenoorbital meningiomas, showed an improved QOL on follow-up. Further objective evaluation of visual fields preoperatively and postoperatively, and correlation with follow-up QOL measures, would be one avenue of research that could provide significant insight into the treatment of skull base tumors.

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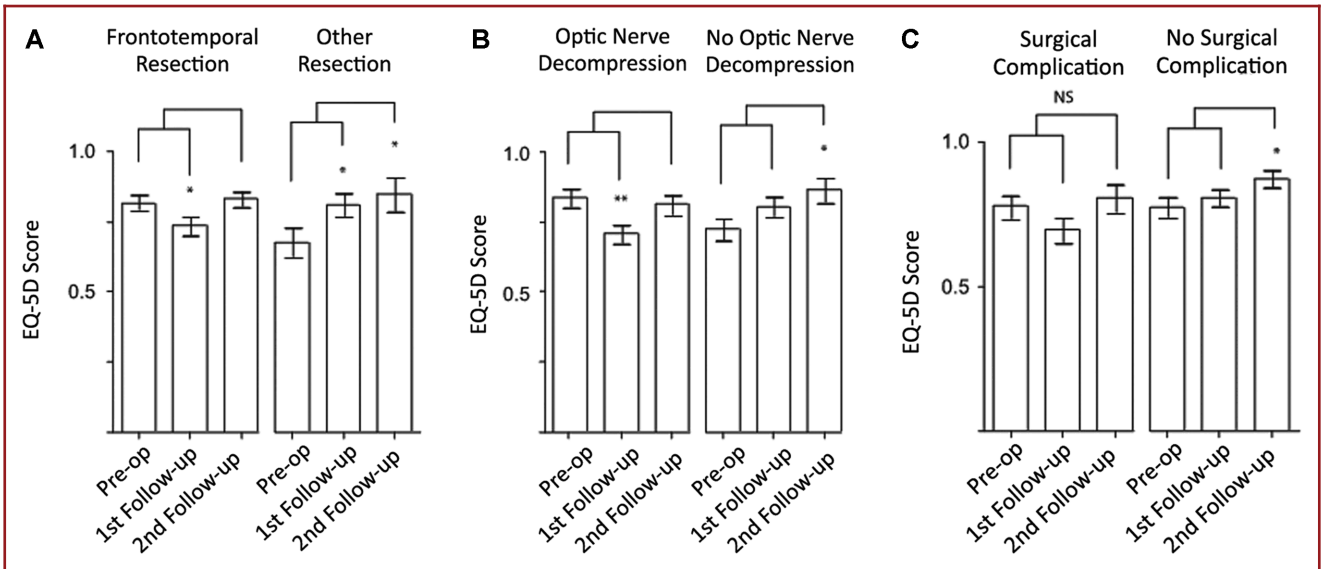


FIGURE 3. *Effect of surgical variables on EQ-5D-3L index score during the follow-up period. Mean (± SEM) EQ-5D-3L scores by* **A**, *surgical approach,* **B**, *optic nerve decompression occurrence, and* **C**, *surgical complication result. *P < .05. ** P < .01. NS, not significant.*

The correlation of cost and QOL remains an important point in neurosurgical treatment options. Patient QALYs significantly improved at 1-yr follow-up for patients with early initial improvement of EQ-5D-3L index scores. Costs per QALY decreased for all groups during each follow-up period but did not differ among groups. A willingness-to-pay threshold target of $50 000 per QALY has been reported for U.S medical drugs and procedures.[22] One major caveat in this study is that the CER was used because a comparative group (eg, medically or radiosurgically managed patients) was not available. Thus, further study to evaluate the role of skull base surgery in meningiomas in relation to alternative treatments is necessary.

Patient-Reported Outcomes in Meningioma

Several studies have assessed QOLs for individuals with meningiomas, but only some of these have reported separate data for skull base meningiomas.[23-29] Dijkstra et al[29] compared patients with grade I meningioma that underwent surgery and adjuvant radiotherapy with matched controls. Patients with meningioma showed significant impairments in executive function, verbal memory, information-processing capacity, psychomotor speed, and working memory. Patients with skull base meningiomas or left-sided lesions were also more likely to have cognitive deficits. These results fit with how tumor location affects neurological function and likely the QOL. Jakola et al[28] found an average improvement in EQ-5D index scores in meningioma patients of 0.06 at 6 wk postoperatively and 0.09 in the long term. Overall, 49% of patients showed improved QOLs, whereas 20% had worse QOL scores, with preoperative scores playing a role in which patients benefitted. This was similar to our results, in which 86.6% of patients showing improved or stable QOLs during follow-up and 13.4% had worse scores. Konglund et al[27] studied 54 elderly patients with meningioma (age ≥ 60 yr); they found improved QOL outcomes compared with other oncological patients, but not compared with the general elderly population. Combes et al[23] evaluated 507 patients with skull base meningioma that underwent either fractionated stereotactic radiotherapy or intensity-modulated radiotherapy. The QOL was unchanged in 47.7% of patients and improved in 37.5%. Kessel et al[24] evaluated 275 meningioma cases and found that patients with tumor progression or symptoms shortly after radiotherapy were the most likely to continue showing lower QOLs at 2 yr. Zamanipoor et al[25,26] performed a meta-analysis of 19 articles evaluating QOLs in patients with meningioma. QOL data were judged to be adequately reported in only 5 of 19 studies. Meningioma patients showed worse QOLs than healthy controls and no difference in QOLs from glioma patients. Radiotherapy and surgical treatment improved short-term QOL levels, but the long-term benefits remained limited compared with control patients, suggesting impaired QOL for meningioma patients regardless of treatment.

These observations present a dilemma for surgeons treating skull base meningiomas. Although the recurrence rate may be diminished with an aggressive resection, aggressive treatment may be associated with a significant early decline in patient QOL. This early decline may be justified for overall tumor control and reduction of recurrence-related deficit in the longer term, but patients should be counseled about the effect so they may anticipate it. These results also emphasize the limitations of

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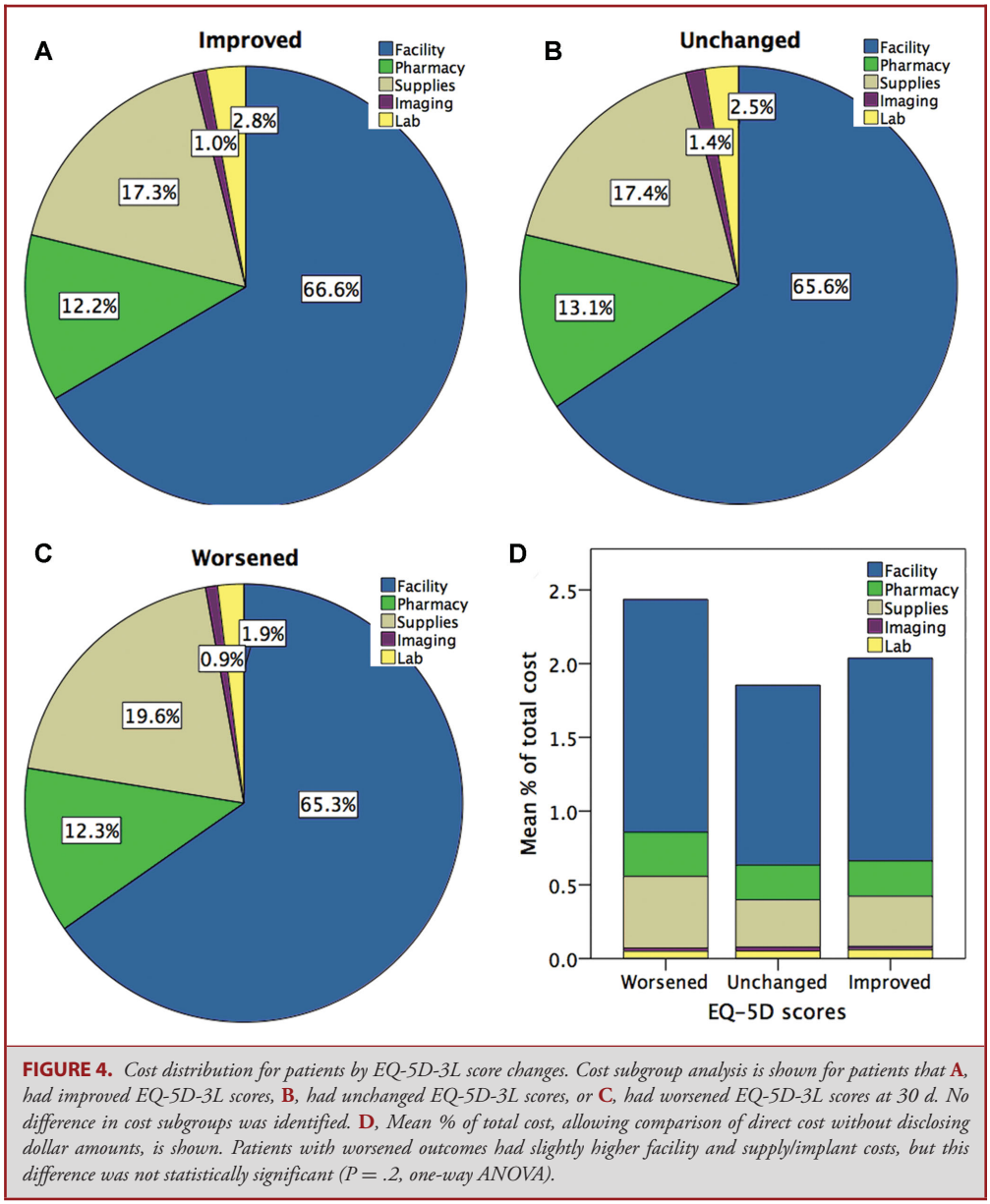


FIGURE 4. *Cost distribution for patients by EQ-5D-3L score changes. Cost subgroup analysis is shown for patients that* **A**, *had improved EQ-5D-3L scores,* **B**, *had unchanged EQ-5D-3L scores, or* **C**, *had worsened EQ-5D-3L scores at 30 d. No difference in cost subgroups was identified.* **D**, *Mean % of total cost, allowing comparison of direct cost without disclosing dollar amounts, is shown. Patients with worsened outcomes had slightly higher facility and supply/implant costs, but this difference was not statistically significant (P = .2, one-way ANOVA).*

using standardized tools such as the EQ-5D-3L questionnaire in assessing optimal patient care and outcome in surgery for skull base meningiomas. Additional neurosurgery- and skull base-specific QOLs are likely needed to capture the nuances of patient neurological function after treatment. The time until follow-up is also important for QOL and is disease specific. Skull base meningiomas are slow growing, with potential for neurological compromise, and postsurgical changes are often transient. The results of this study suggest that patients should be reassured at 30-d follow-up visits regarding potential neurological improvement or stabilization.

Subgroup Analysis

We sought to identify the clinical and surgical factors that contribute to the patient-perceived QOL before and after skull base meningioma resection. Female sex, lack of proptosis, nonfrontotemporal approaches, optic nerve decompression, and the absence of surgical complication seemed to correlate with improved scores. Improvement in the self-care subdomains of EQ-5D-3L seemed to correlate with improved overall scores. The potential to reduce optic nerve compression, maintain visual field alignment, and preserve vision likely has a strong association with preserving overall activities of daily living and QOL.[7] The

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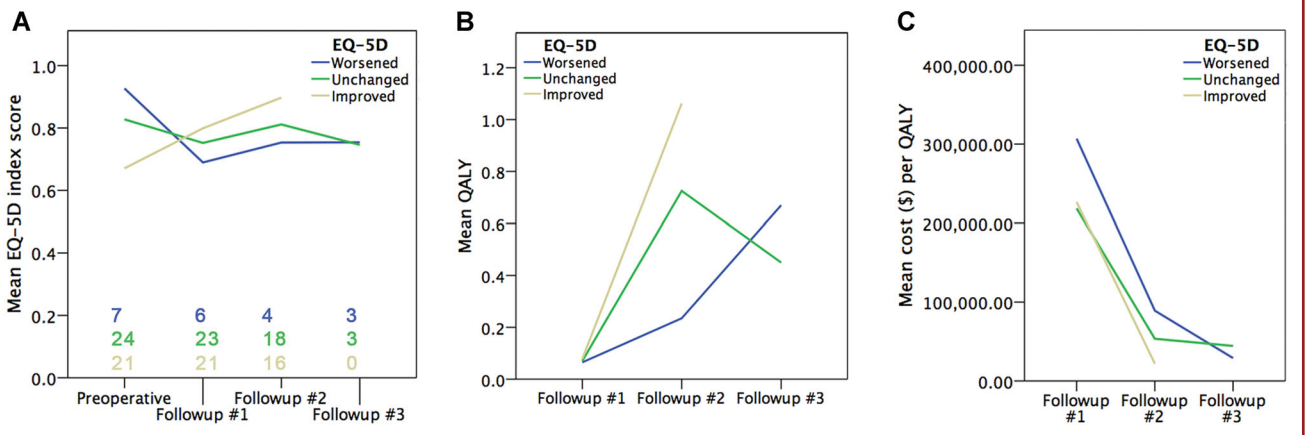


FIGURE 5. *EQ-5D index score, QALY, and cost per QALY depending on EQ-5D score changes.* **A**, *Patients with improved EQ-5D-3L index scores (mean 0.80 ± 0.19) at 30 d had significantly lower initial scores (mean 0.67 ± 0.23) than the other groups, and these patients also improved at 1 yr (mean 0.90 ± 0.14; P < .05). At follow-ups #2 (1 yr) and #3 (longer), EQ-5D-3L scores were not significantly different among groups. The numbers of patients per group are represented across follow-up.* **B**, *Patients with improved outcomes showed the highest average QALY. There was a significant difference in QALYs at 1 yr among groups (P = .04, one-way ANOVA), which resulted from the greater QALYs in the improved patient group.* **C**, *Cost per QALY decreased over time for all patients. There was no difference in cost per QALY at follow-up time points. The overall mean cost per QALY at the last follow-up time point was $27 731.06 ± 22 050.58.*

TABLE 4. Evaluation of Cost-Effectiveness Ratios for Patient Outcome

Variable	QALY (Mean ± STD)	*P*-value	Cost/QALY at 1 yr ($) (Mean ± STD)	*P*-value
Improved				
Yes	1.06 ± 0.7	.05	21 958 ± 15 544	.05
No	0.64 ± 0.52		59 983 ± 85 493	
Surgical complication				
Yes	0.82 ± 0.61	.98	58 312 ± 59 419	.6
No	0.83 ± 0.79		41 436 ± 71 032	
Medical complications				
Yes	0.32 ± 0.22	.08	61 289 ± 46 238	.7
No	0.88 ± 0.68		43 220 ± 72 474	
Extent of resection				
Simpson grades I-III	0.71 ± 0.49	.1	31 675 ± 28 569	.9
Simpson grades IV-V	1.11 ± 0.82		22 411 ± 18 577	
Disposition				
Home/self-care	0.89 ± 0.66	.3	33 653 ± 33 706	.09
Home health	0.17		93 984	
Acute rehab	0.52 ± 0.34		1 000 014 ± 16 852	
Length of stay				
≤5 d	0.56 ± 0.37	.03	25 406 ± 26 587	.03
>5 d	0.97 ± 0.71		75 800 ± 100 688	

invasion of the tumor in the visual region may also represent more aggressive tumors, which are associated with greater surgical complexity and more complications, which can lower patient-reported QOL scores. Our overall surgical and medical complication rates were 11.5% and 3.8%, respectively, similar to those of previous skull base studies.[5] Surprisingly, other factors that could have potentially altered QOLs—including hospital length of stay, tumor location, and patient age—did not, in fact, affect the reported QOLs.

Limitations

Overall, the sample size was limited for this study, thus hindering the ability to fully correlate patient subgroups with changes in EQ-5D-3L scores. There was variability in tumor locations and surgical approaches for this group, which makes the study sample more heterogeneous for analysis. The time points at which the EQ-5D-3L surveys were completed also slightly varied for patients; however, factoring in the time from the preoperative visit until the new follow-up survey allowed calculation of

QALYs, which allow for the length of time during follow-up. A potential bias in this study could arise from a small subset of patients who did not have follow-up 1 yr after surgery. A sensitivity analysis with the lowest and highest cost per QALY values entered for missing data showed no changes in the study findings. This absence of long-term follow-up could alter outcomes by reducing the difference in EQ-5D scores in some patient groups. We also could not perform an ICER calculation because of the lack of a comparative treatment group, limiting the evaluation of a willingness-to-pay threshold of $50 000/QALY in this study, as discussed in the cost-effectiveness literature.

CONCLUSION

To our knowledge, there has not been a specific study to date addressing EQ-5D-3L index scores or cost-effectiveness analysis specifically in patients with skull base meningiomas. Overall, most patients showed improved or stable QOLs during follow-up, and changes at 30 d seemed to predict outcome at 1 yr. Vision seems to affect the QOL more than other factors, and thus vision preservation should be a key part of any surgical plan. Although the treatment of skull base meningiomas remains expensive, longer follow-up suggests these costs will decline to levels similar to those of other medical treatments and surgical procedures. Long-term follow-up, evaluation of other QOL metrics, and comparison of adjuvant therapies can certainly be additional areas of study for skull base meningiomas.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgment

We thank Kristin Kraus, MSc, for editorial assistance with this paper.

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The Spectrum of Trigeminal Neuralgia Without Neurovascular Compression

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Received, May 10, 2018.
Accepted, January 29, 2019.
Published Online, April 25, 2019.

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BACKGROUND: In trigeminal neuralgia type 1 (TN1), neurovascular compression (NVC) is often assumed to be the pain initiating mechanism. NVC can be surgically addressed by microvascular decompression (MVD). However, some patients with TN1 present without NVC (WONVC).

OBJECTIVE: To characterize and analyze the clinical spectrum of a TN1 patient population WONVC.

METHODS: A retrospective chart review of patients presenting with TN1 between 2007 and 2017 was performed. Patients who were potential candidates for MVD surgery underwent high-resolution imaging with 3-dimensional (3D) reconstruction to address the presence, or absence, of NVC. Demographic data about the populations with NVC (WNVC) and WONVC were collected.

RESULTS: Of 242 patients with TN1, 32% did not have NVC. Patients WONVC were on average 10.6 yr younger than those WNVC. TN1 onset in patients WONVC was more frequent below 48.7 yr, and the opposite was found in patients WNVC. Compared to patients WNVC, those WONVC were predominantly female (odds ratio 4.8), on average were 4 yr younger at symptom onset (34.7 yr) and 7.8 yr younger at first clinic visit, and had a 3.7 yr shorter symptom duration.

CONCLUSION: Patients presenting with TN1 WONVC were predominantly females in their mid-30s with short symptom duration. In the absence of NVC, this subgroup of TN1 patients has limited surgical options, and potentially a longer condition duration that must be managed medically or surgically. This population WONVC might provide insights into the true pathophysiology of TN1.

KEY WORDS: Trigeminal neuralgia, Neurovascular compression, Trigeminal, Neuralgia\pathophysiology, Cranial nerve neuralgia, Pain, Trigeminal neurovascular compression

Neurosurgery 85:E553–E559, 2019 DOI:10.1093/neuros/nyz048 www.neurosurgery-online.com

Trigeminal neuralgia type 1 (TN1)[1] or classical trigeminal neuralgia[2] is defined as unilateral facial pain occurring in one or more divisions of the trigeminal nerve in a paroxysmal, severe, electrical, and triggerable pattern. In the TN1 classification, this type of pain accounts for more than half of the patient's facial pain. The pathophysiology of TN remains incompletely understood, since the publication of the neurovascular compression (NVC) theory by Jannetta,[3] it has become the putative mechanism. This mechanism was further supported by the frequent presence of NVC among patients with TN[4-6] and the durability of the relief of pain after microvascular decompression (MVD).[7,8]

Compression of the trigeminal nerve entry zone by an artery may result in neuronal hyperexcitability.[9,10] However, reports of TN without NVC (WONVC) have increased both at first clinical presentation and upon TN recurrence.[5,11,12] Furthermore, NVC in the absence

ABBREVIATIONS: 3D, 3-dimensional; **IRB,** institutional review board; **MS,** multiple sclerosis; **MRA,** magnetic resonance angiography; **MRI,** magnetic resonance imaging; **MVD,** microvascular decompression; **NVC,** neurovascular compression; **SD,** standard deviation; **SEM,** standard error of the mean; **TN1,** trigeminal neuralgia type 1; **WNVC,** with NVC; **WONVC,** without NVC

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of TN has been demonstrated in 17% of asymptomatic individuals and contralateral to the symptomatic side in 43% of TN1 patients.[12] That is, NVC alone does not seem to be sufficient to cause TN1, nor does it appear to be essential. There is no doubt that NVC plays a role in the pathogenesis of TN, however for each TN1 patient with NVC (WNVC) there are 400 asymptomatic individuals WNVC on imaging.[12] Therefore, it is reasonable to assume that there are other predisposing factors at play in those individuals who develop TN1. In these cases, NVC could act as a trigger in individuals where a predisposition to develop TN1 already exists.[13]

Our objective was to determine if patients WONVC represent a different subgroup of TN1, by retrospective review of our entire TN1 patient population over the past decade.

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METHODS

Study Design and Setting

A waiver of consent for the study protocol was approved by the local institutional review board (IRB). A retrospective chart review of patients 18 yr of age and older diagnosed clinically with TN based on the Burchiel classification of facial pain,[1] presenting between 2007 and 2017 to a single neurosurgeon, was performed.

Participants

All identified 242 patients had TN1 defined as idiopathic, episodic, lancinating pain that lasted seconds, with pain-free episodes between attacks. When this type of pain was rated as encompassing more than half of the patient's facial pain, a TN1 diagnosis was clinically assigned. Patients with TN2, defined as having predominantly aching, throbbing, or burning pain that represented >50% of the patient's pain, were excluded from analysis. Patients with a diagnosis of multiple sclerosis (MS) or having signs or symptoms of MS were also excluded. To address potential postoperative development of MS after their initial presentation and assignment of a diagnosis of TN WONVC, patients were contacted by a mailed questionnaire and a phone interview (with IRB approval). Patients were asked if they had ever been diagnosed with MS and if they ever had undergone a work-up for MS including a lumbar puncture, magnetic resonance imaging (MRI), or other investigations.

All patients with TN1 had undergone diagnostic high-resolution 3T magnetic resonance imaging/angiography (MRI/MRA). Three-dimensional (3D) reconstructions were generated from the MRI/MRA fusion to confirm or infer the presence of NVC.[5,12] Neurovascular compression was defined using the Sindou classification: 1 = contact, 2 = compression, 3 = distortion.[6] Intraoperative findings and postoperative review of operative video were used to confirm imaging results when available. Demographic data collected included the following: gender, age at presentation to clinic, reported age of symptoms onset, symptom duration, presence or absence of NVC, and medications for TN and reported response. Age at symptom onset was used to define the age distribution of the patient population.

Statistical Methods

Patient ages were aggregated by decade. A Gaussian curve was derived using a least squares fit method. Comparison of Gaussian curves was performed by an extra sum-of-squares *F*-test. Means were compared by unpaired Student *t*-tests. Welch's correction was applied if variances were different between groups. Answers from the MS questionnaire and phone interview were analyzed by Mann–Whitney tests. The Fischer exact test was used for contingency analysis. A *P*-value of <.05 was considered significant. Data is presented as mean ± standard error of the mean (SEM) or standard deviation (SD).

RESULTS

Descriptive Data

Vascular Compression and Age of Symptom Onset

In total, 32% of patients (n = 77/242) had no visible arterial compression of the trigeminal nerve as determined by MRI/MRA analysis. The mean age (±SEM) at symptom onset for patients WONVC was 45.5 ± 1.7 yr, which is 10.6 yr younger than those WNVC, which was 56.1 ± 1.1 yr (Figure 1A; $P < .0001$). The distributions of patient age at symptom onset between patients WONVC and patients WNVC best fit two Gaussian curves (Figure 1B, mean and amplitude significantly different, $P = .002$) intersected at 48.7 yr. At <48.7 yr, patients were more likely to present WONVC. To better characterize the TN1 WONVC population, we focused on patients whose symptom onset was younger than 49 yr of age.

TN at <49 yr of Age

The TN1 (<49 yr of age population; n = 89) composed 46 patients WONVC (60%; n = 46/77) and 43 patients WNVC (26%; n = 43/165); this difference was statistically significant ($P < .0001$). Age at TN1 symptom onset in this patient subset was 4 yr younger for patients WONVC (Figure 2A; mean 34.7 ± 1.3 vs 38.8 ± 1.2 yr, $P = .02$). Age at presentation to clinic was 7.8 yr younger for patients WONVC compared to those WNVC (Figure 2B; means 38.6 ± 1.5 vs 46.4 ± 1.6 yr, $P = .0007$). Symptom duration before referral to neurosurgery in patients WONVC was significantly shorter by 44.7 mo than for those WNVC (Figure 2C; mean 46.6 ± 9.8 vs 91.3 ± 15.9 mo, $P = .02$, WONVC and WNVC, respectively). Symptom duration increased as patient age at visit increased irrespective of the presence or absence of NVC (Figure 2D). However, patients with an onset of TN1 at younger ages were not found to have longer symptom duration before referral (Figure 2E; Figure 2 ±SEM). Patients younger than 49 yr of age WONVC were more likely to be female with an odds ratio of 4.8 (Figure 3A; $P = .002$). This female predominance was not seen in patients older than 49 yr of age (68% WONVC vs 61% WNVC, $P = .54$ by Fischer's exact test). Intraoperative findings were available for 36 patients WONVC and 38 patients WNVC and in this subset corroborated with MRI findings.

Medications

Medications prescribed for TN included the following: carbamazepine (52% WONVC, 47% WNVC), oxcarbazepine (11% WONVC, 21% WNVC), gabapentin (41% WONVC, 47% WNVC), pregabalin (9% WONVC, 5% WNVC), topiramate

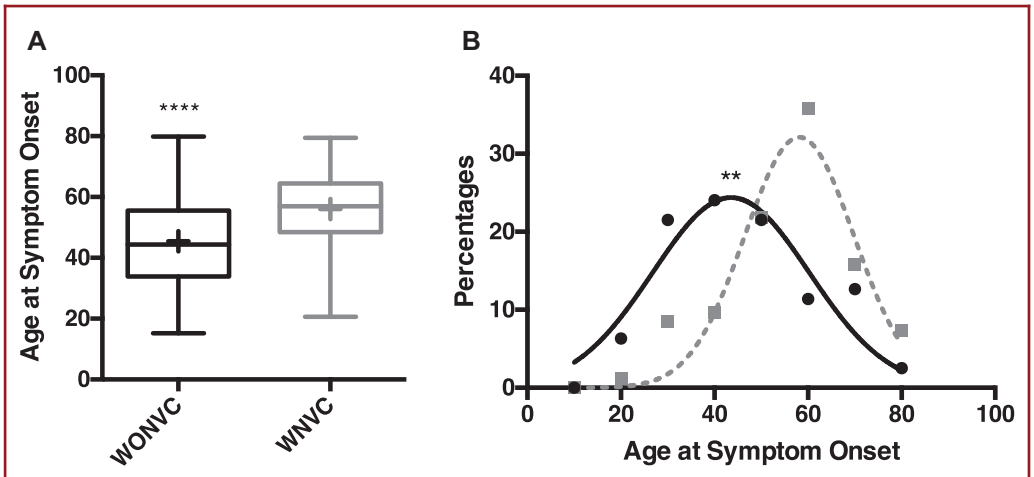


FIGURE 1. *Age at symptom onset in patients WONVC and WNVC.* **A**, *Age of symptom onset in patients with and without neurovascular compression.* **** *P* < .0001, *unpaired Student t-test.* **B**, *Relative frequency in percentages of age of symptom onset aggregated by decade in patients WONVC (black, mean 43.5,* R^2 *0.86) and WNVC (grey, mean 58.2,* R^2 *0.91). Gaussian curve mean and amplitude statistically different by extra sum-of-squares F test (** P = .002). Curves cross at 48.7 yr.*

(7% WONVC and WNVC), and baclofen (2% WONVC and WNVC). Data was not available for 2 patients in each group. Two patients WONVC refused medications. Response to the above medications was similar between patients WONVC and WNVC (Figure 3B). There was no difference between symptomatic sides (Figure 3C) and trigeminal branches involved (Figure 3D).

Other Analyses

Multiple Sclerosis

Among all TN patients WONVC (n = 77), data about MS onset postsurgery was available for 46 patients (60%). A total of 3 patients declined to answer, 26 patients could not be contacted despite multiple attempts, and 2 patients were deceased. The average age at time of presentation at clinic visit was 51.7 ± 15.7 yr vs 48.5 ± 17.4 yr (survey responders vs nonresponders, mean ± SD, P = .44). In total, 83% of survey responders were female compared to 71% of nonresponders (P = .27). The average duration of symptoms until distribution of the MS survey was 10.4 ± 6.0 yr vs 11.4 ± 7.1 yr (responders vs nonresponders, mean ± SD, P = .59). The average follow-up time since the first clinic visit was 5.9 ± 2.8 yr vs 6.5 ± 3.0 yr (survey responders vs nonresponders, mean ± SD, P = .31). Overall, the demographics of responders compared to nonresponders were not statistically different.

No survey responders had been diagnosed with MS subsequent to surgery. Fourteen patients (30%; n = 14/46) had undergone investigations for MS prior to surgery without fulfilling the diagnostic criteria of MS. Thirteen were female. One male patient had a diagnosis of chronic inflammatory demyelinating polyneuropathy and chronic lymphocytic leukemia, and one patient had been informed that investigations were inconclusive for relapsing-remitting MS 17 yr prior to surgery. Despite a significant loss to follow-up, there is no indication from the data analysis that MS ultimately occurs in the population of younger patients with TN1 WONVC, or, more importantly, that TN1 is a harbinger of MS in this younger, predominantly female, population.

DISCUSSION

Key Results

The findings of this study reveal a unique patient population with clinical TN1 WONVC. This TN1 WONVC population is predominantly composed of younger females, who are in their mid-30s. This is in contrast to the older age (57-61 yr) of patients with TN1 WNVC.[7,14] A reconsideration of the TN1 age distribution, recognizing a significant presence of TN1 WONVC in younger patients, is warranted. An analysis of this younger population may provide insight into the mechanism of TN1.

Given that MVD is not relevant to this younger group of TN1 WONVC patients, surgical therapy must consist of other procedures such as trigeminal rhizotomy or rhizolysis. These procedures can have an increased incidence of trigeminal dysesthesias or pain especially if repeated.[15,16] Therefore, unless alternative therapies can be developed, younger patients with TN1 may ultimately have a higher likelihood of developing refractory chronic facial pain.

The incidence of TN1 in patients <50 yr of age is significantly less than in patients >60 yr of age.[17] Historically, a younger female patient with TN1 would likely have been referred for a MS evaluation. In fact, many of the younger female cohort here were tested for MS and that diagnosis was not supported or

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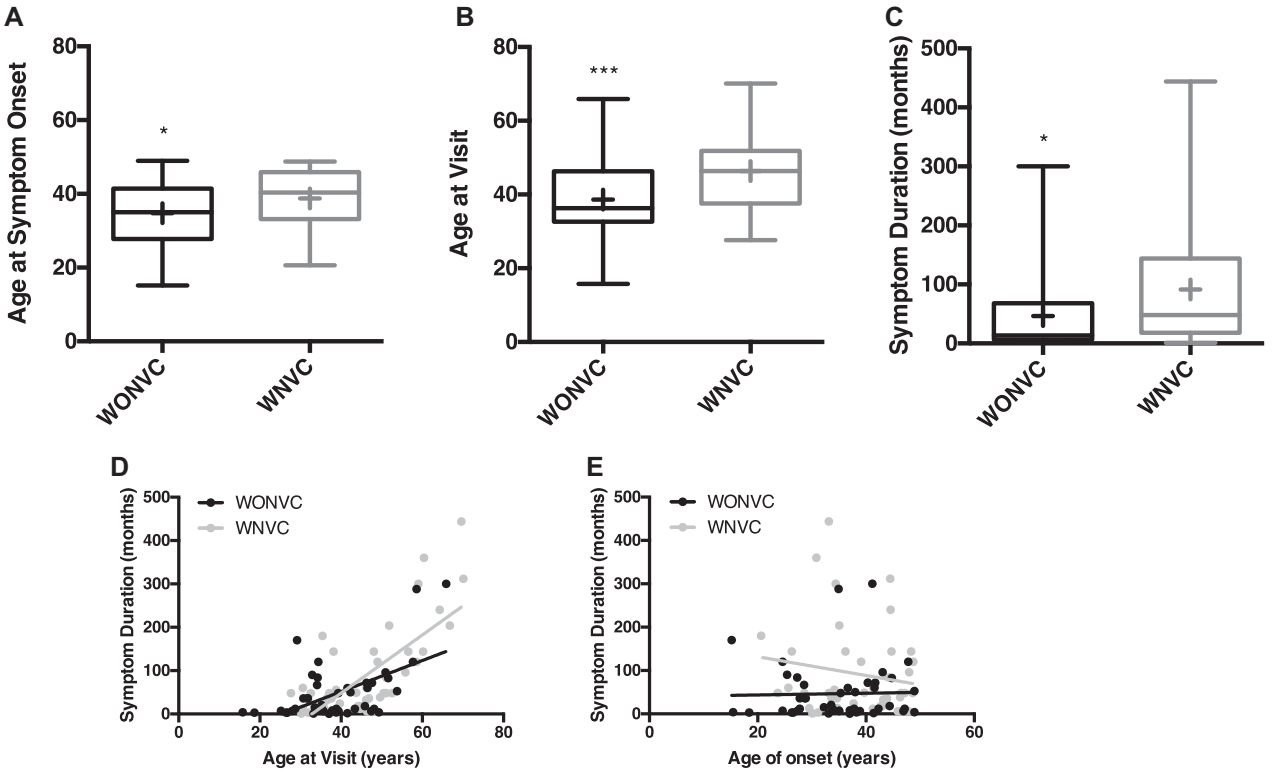


FIGURE 2. *Symptom duration in patients younger than 49-yr-old WONVC and WNVC.* **A**, *Box and whiskers plot of age at symptom onset in patients with symptom onset prior 49 yr WNVC or WONVC. Symptoms in patients WONVC started 4 yr before patients WNVC. Mean 34.7 ± 1.3 vs 38.8 ± 1.2 yr, median 35.0 vs 40.4 yr, WONVC vs WNVC, *P = .02 by unpaired t-test Welch's correction.* **B**, *Box and whiskers plot of age at visit in patients whose TN symptoms started before 49 yr of age. Age at visit in patients WONVC was younger by 7.8 yr compared to patients WNVC. Mean 38.6 ± 1.5 vs 46.4 ± 1.6 yr, median 36.3 vs 46.4 yr, WONVC vs WNVC. ***P = .0007 by unpaired t-test.* **C**, *Box and whiskers plot of symptom duration prior to visit to neurosurgery reveals a shorter duration by 44.7 mo in patients WONVC. Mean 46.6 ± 9.8 vs 91.3 ± 15.9, median 13.5 vs 48.0, *P = .02 by unpaired t-test Welch's correction.* **D**, *Symptom duration in function of age at visit. Longer duration of symptoms is encountered among older patients. Linear regression in patients WONVC: slope 3.6, Y-intercept −91.6, R^2 0.31. Linear regression in patients WNVC: slope 6.7, Y-intercept −220.0, R^2 0.49. Slopes significantly different.* **E**, *Symptom duration in function of age of onset. Slopes of linear regression from both groups were not significantly different from zero.*

established. Further, among the MS questionnaires received, none of our younger patients with TN1 have gone on to develop MS. Therefore, we would argue that the results presented here are unlikely to be secondary to either undiagnosed, or a *forme fruste* of MS. Based on a systematic review, only 3.7% of MS patients develop TN.[18] Fifteen percent of MS patients with TN present with TN prior to being diagnosed with MS.[19,20] As published in the North American Research Committee on Multiple Sclerosis Registry, TN occurred 8 yr prior to the MS diagnosis and 4 yr after onset of MS symptoms for patients presenting with TN prior to the diagnosis of MS.[20] Our follow-up covers a similar period and yet the majority of our population was never diagnosed with MS. Based on our results it would appear that TN1 patients WONVC generally do not develop MS despite the fact that the majority are young and female. As a retrospective study, the study is limited in that longer follow-ups and a larger population are needed to definitively answer this question. The study also relied on accurate clinical reporting and individual patient recall, which may be inaccurate and subject to biases. Nevertheless, our study describes a new and distinct population of patients with TN1 that may have previously been either overlooked or underemphasized, but certainly underdiagnosed.

Validity

TN1 remains a phenotype based on symptomatology. Since the description of NVC in TN1 patients,[3] NVC, whether arterial or venous, has effectively been assumed to be the *sine qua non* of classic TN. However, there has been a persistent incidence of TN1 WONVC published in MVD series, ranging from 3.1% to 20%,[3,14,21-26] and here we report an incidence of 32%. Patients with TN1 discovered to have no NVC at the time of surgery would have been typically treated by overt rhizotomy

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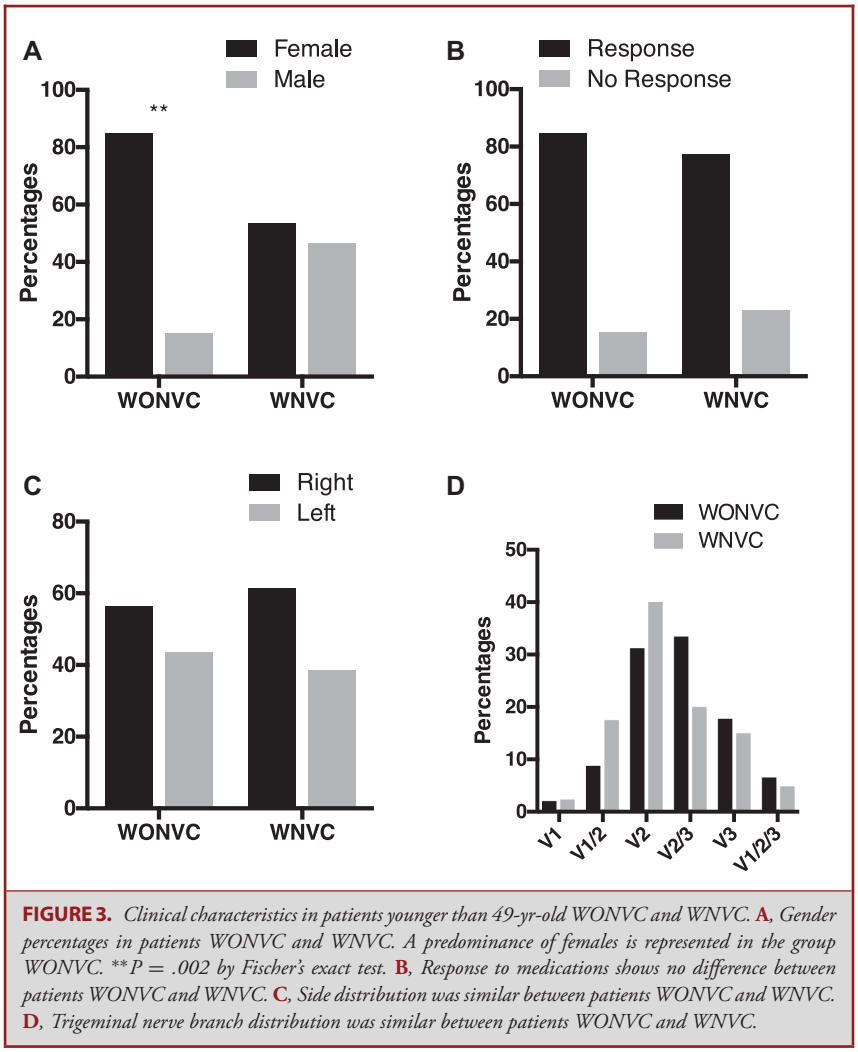


FIGURE 3. *Clinical characteristics in patients younger than 49-yr-old WONVC and WNVC.* **A**, *Gender percentages in patients WONVC and WNVC. A predominance of females is represented in the group WONVC. **P = .002 by Fischer's exact test.* **B**, *Response to medications shows no difference between patients WONVC and WNVC.* **C**, *Side distribution was similar between patients WONVC and WNVC.* **D**, *Trigeminal nerve branch distribution was similar between patients WONVC and WNVC.*

of the trigeminal nerve near the root entry zone. A modification of this ablative procedure, named internal neurolysis, has also shown long term pain control in patients WONVC.[16] Internal neurolysis is an effective treatment for TN1 WONVC, appears to be more effective than Gamma Knife surgery (Elekta AB, Stockholm, Sweden), at least as effective as partial sensory rhizotomy, and is likely more durable than radiofrequency ganglionolysis.[16] Briefly, when no compression is found, the trigeminal nerve itself is longitudinally divided along its fibers, into 5 to 10 bundles from the root entry zone to the petrous bone, both the portio minor and portio major are included in the neurolysis.[16] We suspect IN is destructive, since patients describe some transient facial numbness, which typically resolves over days to weeks.

Increasing evidence suggests that TN may originate from an underlying process, which requires initiation by a trigger such as NVC. Relapse of TN after MVD has been shown without recurrence of compression.[11,27] The sensitivity of imaging as a predictor of NVC for both TN1 and TN2 has been reported as 96%, and the specificity of imaging findings for patients with TN1 and TN2 were 90% and 66%, respectively.[11] NVC has been identified in asymptomatic patients both by imaging and anatomically: 17% of a non-TN patient population by MRI[12] and 60% from cadaveric anatomical analysis.[28] Since TN prevalence ranges between 0.07% and 0.3%, NVC is vastly more common than the reported occurrence of TN,[29-31] to the extent that over 99% of trigeminal NVC is asymptomatic. It appears that if, in fact, TN originated solely from NVC, it would occur approximately a 100 times more frequently than its current prevalence. For these reasons, we propose that the underlying mechanism responsible for TN is more complex than a single factor such as NVC, requiring an underlying predisposition. By this logic, TN may also be a condition with multiple origins, and multiple triggers.

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The leading theory for the pathophysiology of TN is the "ignition" hypothesis proposed by Devor and Rappaport in 2002.[9,10,32] The ignition hypothesis proposes three key elements in the genesis of TN: a trigger, an amplifier, and a stop mechanism. The trigger mechanism may be an ectopic action potential generator such as an area of axonal demyelination caused by NVC, which in turn may provoke sustained hyperactivity in trigeminal ganglion neurons in the form of high-frequency after-discharges. Both of these preconditions have been demonstrated experimentally in the laboratory and in patients with TN.[9,10,33] According to this theory, triggering involves ectopic high-frequency activity in the trigeminal nerve root producing retrograde activation in the trigeminal ganglion, which in turn depolarizes ganglionic cell bodies with the release of excitatory neurotransmitters into the intercellular space of the ganglion. Neurotransmitter release amplifies the effect of what might be only a single locus of axonal hyperactivity, by producing a chain-reaction in the ganglion with rapid depolarization of adjacent cell somata, leading to a regenerative, but ultimately self-limited, wave of depolarization in the ganglion.[34,35] This cellular depolarization, in the absence of synapses, has been shown in some cases to be purinergic between dorsal root ganglion neurons and surrounding satellite cells[36,37] and requires oscillations of membrane potentials.[38] This wave of depolarization can cross trigeminal divisions, and is perceived as a lancinating pain sensation, which is described as "shocking" or "stabbing."[39] The stop mechanism would then be the refractory period of the ganglionic cell bodies after a brief period of pathological hyperactivity.[40]

Although NVC is an attractive origin for postganglionic trigeminal demyelination, and the possible attendant pathophysiology of the ignition hypothesis, our data would suggest that it is not essential for the development of clinical TN1. These results suggest that there may be predisposing factors that allow more than one origin for TN1, since it appears that younger patients, predominantly women, may have a different form of TN1 which does not require NVC.

Limitations

Limitations to this study include its retrospective nature, with inherent disadvantages and bias, and performance at a single institution.

CONCLUSION

TN1 WONVC occurs in nearly one third of patients presenting with TN1. Patients WONVC are younger than the average TN population and are predominantly female by a factor of almost five to one. Evidence also indicates that NVC of the trigeminal nerve is so common, that the incidence of TN1 related to NVC is only a "trace effect" in much less than 1% of individuals WNVC. We propose that TN1 occurs on the background of one or more factors, yet to be described, predisposing individuals to develop TN1. It may well be that TN1 is a syndrome with more than one origin. Further investigations, such as genetic and neuroimaging studies, may provide insight into determining the pathophysiology of TN and facilitate the development of effective therapies.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We would like to acknowledge the Cody German, MS and Ashraf Samhan, BS for assistance with data collection. We thank Shirley McCartney, PhD, for editorial assistance.

COMMENT

The authors of this analytic paper reviewed a large single-institution experience with typical trigeminal neuralgia (TN). Based on presence or absence of radiographic evidence of vascular compression of the trigeminal nerve root they concluded that there is a distinct cohort of younger TN patients who do not have clear root compression (and therefore would not benefit from microvascular decompression [MVD]) and that the vast majority of these patients (>80%) are women.

Among other things, this finding may explain lower success rates of MVD in younger female patients – MVD is unlikely to help if there is no compression in the first place. Unfortunately, this eliminates the only non-destructive surgical option available to TN patients – and with this limitation in treatment choices, an emphasis should be placed on efficacy and longevity of surgical outcomes as the young age of patients will likely translate into a need in multiple repeated interventions, at least until a cure for TN is discovered.

Female preponderance in the subgroup of TN patients without obvious neurovascular compression deserves additional investigation. In addition to genetic factors that may make certain patients more susceptible to vascular compression, there may be another set of genes, possibly gender-linked, that is responsible for TN symptoms through a different pathogenetic mechanism. With rarely described (but frequently observed) symptomatic improvement of TN during pregnancy, one may suspect that hormonal changes also contribute to TN presentation.

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Hearing Response Following Internal Auditory Canal Decompression in Neurofibromatosis Type 2

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Received, May 2, 2018.
Accepted, February 27, 2019.
Published Online, March 19, 2019.

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BACKGROUND : Hearing response following an osteodural decompression of the internal auditory canal (IAC) is controversial.
OBJECTIVE: To evaluate the course of auditory brainstem responses (ABRs) and the early hearing response during the first year following IAC decompression for small to medium-sized vestibular schwannomas occurring in neurofibromatosis type 2 (NF2).
METHODS: Retrospective chart review of middle fossa craniotomy for IAC osteodural decompression in NF2-related vestibular schwannomas.
RESULTS: Twelve NF2 patients were operated on from 2011 to 2016 for IAC decompression. All had NF2 according to the Manchester criteria. All had a progressive change of their ABRs documented from the diagnosis of NF2 over a mean period of 6.25 [0.36;10.9] yr. Treatment was proposed to stop hearing progression based on the speech discrimination scores (SDSs; n = 4) or for hearing maintenance (n = 8). In patients with prior hearing progression, hearing responses were observed in 3 of the 4 patients during the first year. One patient kept on progressing. In the hearing maintenance group, the SDSs remained stable. SDSs improved from 85% [20-100] to 92.5% [60-100] on average (n = 12) and from 55% [20-80] to 77.5% [50-100] in the hearing progression group (n = 4). ABRs improved in 4 patients following decompression.
CONCLUSION: IAC decompression allows early objective hearing responses in select patients. We suggest that the procedure should be offered to patients with hearing progression based on their SDSs and/or associated progressive increases in their wave III and V latencies on ABRs.

KEY WORDS: Acoustic neuroma, Deafness, Hearing, Middle fossa craniotomy, Neurofibromatosis type 2, Vestibular schwannoma

Neurosurgery 85:E560–E567, 2019 DOI:10.1093/neuros/nyz057 www.neurosurgery-online.com

The management of hearing is challenging in patients presenting with neurofibromatosis type 2 (NF2). Hearing level is altered in a large majority of vestibular schwannoma (VS) from presentation (reported in up 90%).[1] The usual audiogram in VS has a high-frequency slope in more than 60%.[1,2] Consequently, VS occurring in the setting of NF2 may lead to complete deafness and the chances to maintain natural hearing are unpredictable. Few predictive factors have been identified to foresee a decline in hearing. Indeed, hearing decline in NF2 is a consequence of numerous metabolic and mechanic aggressions to the cochlea and/or the cochlear nerve. Approaches to hearing rehabilitation have therefore evolved and diversified and include air conduction hearing aids, cochlear implantation, and auditory brainstem implantation. Accordingly, Tysome et al[3] proposed an algorithm for guiding the choice of rehabilitation. However, physicians lack options to support the maintenance of natural hearing. In early research, internal auditory canal (IAC) decompression via a middle fossa craniotomy

ABBREVIATIONS: ABR, auditory brainstem response; **AHL,** asymmetric hearing loss; **CSF,** cerebrospinal fluid; **FLAIR,** fluid attenuated inversion recovery; **IAC,** internal auditory canal; **MFC,** middle fossa craniotomy; **MRI,** magnetic resonance imaging; **NF2,** neurofibromatosis type 2; **PTA,** pure tone average; **SDS,** speech discrimination score; **SSD,** single-sided deafness; **TLC,** translabyrinthine craniotomy; **VS,** vestibular schwannoma

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(MFC) approach was proposed as an alternative to tumor removal.[4] In this first report, an improvement in hearing assessed with speech discrimination scores (SDSs) was observed in at least 3 of the 8 reported cases. Using this technique, the mean period of hearing maintenance was 2.1 yr after surgery, as reported in an updated series from Slattery et al.[5] Recently, other groups replicated the technique and were able to confirm its safety. However, they failed to reproduce the hearing response.[6] As an alternative, bevacizumab was proposed in progressive VS on the only hearing ear.[7] Hearing responses were reported either in adults or pediatric patients,[8,9] and these reports suggested that it could be considered a crucial step before eliciting a hearing rehabilitation implantable device.

In this study, we chose to focus on evaluating early hearing outcomes during the first year following decompression of the IAC through an MFC approach for small to medium-sized vestibular schwannomas occurring in the setting of NF2.

METHODS

Population

This was a retrospective study based on a cohort of 110 NF2 patients who were followed in a dedicated NF2 clinic. Patients were identified from all diagnosed cases of NF2 followed in the clinic starting from 1997. This study is based on a retrospective chart review that did not interfere with the usual treatment plan and was carried out in agreement with the local institutional review board in compliance with the French regulations for research on humans including individual patient consent. The charts of all patients who underwent a middle fossa decompression of the IAC for a VS occurring in the setting of NF2 between 2011 and 2016 were retrospectively reviewed. All VSs were evaluated using magnetic resonance imaging according to the protocol described in Picry et al.[10] The study primarily aimed at evaluating the hearing response during the first year following decompression ("early hearing response") in patients presenting with progressive alteration of their auditory brainstem responses (ABRs) over the course of regular follow-up. As a secondary endpoint, we aimed at describing the course of hearing over a longer period of time following decompression.

Surgical Technique

All surgeries were performed in a dedicated department for otoneurosurgery. Patients were prepared, and a Nerve Integrity Monitoring (NIM, Medtronic, Dublin, Ireland) was used to monitor the facial nerve during surgery. Auditory monitoring was obtained using the dedicated intraoperative ABR software developed by Intelligent Hearing System (Intelligent Hearing System, Miami, Florida). This allowed continuous auditory monitoring with ABR obtained every 20 s. We followed a routine technique to approach the IAC after systematic identification of the blue line of the superior semicircular canal. Drilling was continued to unroof the posterosuperior surface of the IAC from Bill's bar to the porus. The dura was opened from the posterolateral end of the IAC to the porus and then anteriorly towards the apex. The cerebrospinal fluid (CSF) was then allowed to release. For closure, care was given to wax any cell opened during drilling. Then, a fascia temporalis harvested at the beginning of surgery and kept in saline was gently interposed between the opened IAC and temporal dura mater. The bone flap was repositioned after the dura had been tacked up using a 5.0 nonabsorbable monofilament suture. The average surgery time was 3 h and 20 min. No secondary facial paresis or CSF leak occurred. The duration of hospital stay was 5 d after surgery. Follow-up occurred at day 12 and 3 mo and every 6 mo afterward. No other complication was reported.

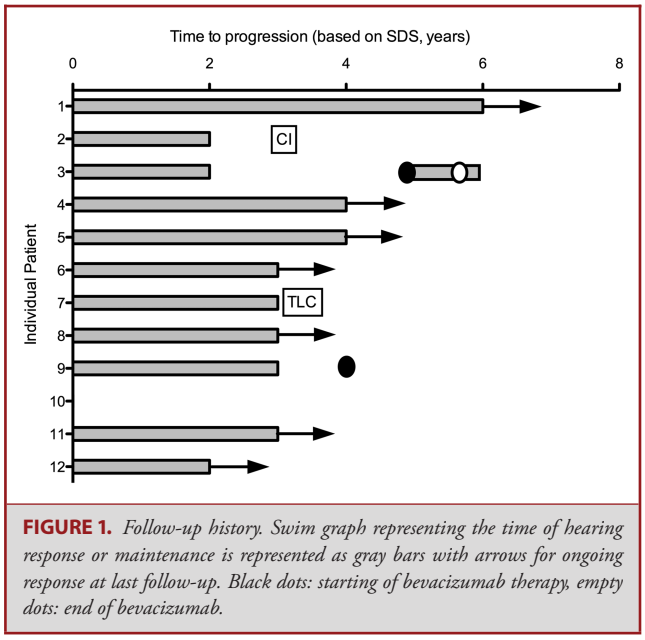


FIGURE 1. *Follow-up history. Swim graph representing the time of hearing response or maintenance is represented as gray bars with arrows for ongoing response at last follow-up. Black dots: starting of bevacizumab therapy, empty dots: end of bevacizumab.*

Hearing Tests

Audiometric assessment included pure-tone thresholds (pure tone average, PTA) and SDS obtained using a closed set of 50 monosyllabic words presented 35 dB above the speech recognition threshold. The standard postoperative follow-up included an audiogram within the first 6 mo and then every 6 mo. ABRs were recorded as part of the routine follow-up. Triplicates of the ABR curves obtained at 90 dB sound pressure level (SPL) were reviewed to identify the amplitude and latency of waves I, III, and V before and after decompression of the IAC.

Outcomes and Statistical Analysis

Hearing response is defined as a significant improvement in SDS. An improvement in SDS follows the criteria proposed for NF2 trials in Plotkin et al.[11] Hearing improvement was defined as a statistically significant increase in word recognition score ($P < .05$) compared with the baseline score.[12] "Patients were eligible for hearing improvement if their pretreatment word recognition score was 94% or lower on a 50-word list (ie, if their baseline hearing allowed for a measurable increase above the upper limit of the critical difference threshold)."[8] Electrophysiologic response is defined by a change in ABR with either a reduction in wave III or V latency by 0.2 ms or greater or by the presence of reproducible wave V peak in a patient with no preoperative identifiable peak (an example is given in Figure 1). Raw data were tabulated using Apple Numbers (Numbers 4.1.1, Apple Inc, Cupertino, California). We then built a contingency table for Fisher's exact testing to compare outcomes in subgroups (Graphpad, Prism 5.0a, La Jolla, California). The results are given as the mean [min; max].

TABLE 1. Clinical Characteristics of Each Individual Patient

	Demographic			Genetic			Audiology		
Case	Age at diagnosis of NF2	Age at surgery	Sex	Genetic NF2 status and affected exon	Genetic severity score according to Halliday et al[40]	Clinical subtype according to Parry et al[41]	Only hearing ear	Preoperative audiometric follow-up (year)	Postoperative follow-up without other treatment (year)
1	33	37	M	–	1A	Mild	No	3.3	6
2	49	53	M	–	1A	Mild	Yes	3.4	2
3	6	9	F	Germline Ex3 familial	2A	Severe	No	3.2	4
4	20	36	F	Germline Ex5	3	Severe	Yes	10.9	4
5	8	14	M	Germline Ex8	3	Severe	No	3.4	4
6	13	27	M	–	1A	Mild	Yes	7.8	3
7	8	16	F	Germline Ex14 familial	2A	Severe	No	8.5	3
8	19	27	M	Germline Ex10 familial	2A	Severe	Yes	9.8	3
9	17	27	M	Germline Ex1	2A	Severe	Yes	10	3
10	9	11	M	Germline Ex1	2A	Severe	Yes	0.36	1
11	25	31	F	–	1A	Mild	Yes	6.2	3
12	40	49	M	Mosaicism Ex6 familial	2B	Mild	No	8.1	2

This table summarizes each individual demographic data and genetic according to the genetic severity score from Halliday et al[40] and clinical subtype according to Parry et al[41] The audiologic presentation and time of follow-up from the diagnosis of NF2 and after surgery are tabulated to emphasize individual history.

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RESULTS

Patient Characteristics

A total of 12 selected patients underwent a decompression through a middle fossa approach (Table 1). The study population consisted of 8 men and 4 women with a mean age of 28 [9;53] yr. All had NF2 according to the Manchester criteria. The mean age at the diagnosis of NF2 was 20 yr [6;40], with 5 patient diagnosed under 18 y/o. There were 4 familial cases. The phenotype was severe in 8 and mild in 4. Genetic testing was carried out on blood leucocyte for all and identified the causing mutation in 7 patients. There was one proven mosaicism at the time of writing among the 5 remaining patients. All had changes in ABR compared to the reference ABR obtained at the diagnosis of NF2. A documented ABR deterioration was identified for all patients and documented over an initial follow-up of 6.25 [0.36;10.9] yr preceding surgery. Only patient 10 had less than 3 yr of preoperative follow-up. This patient was referred from another distant center with no available reference ABR. On top of electrophysiologic deterioration, all had increased their PTA and 4 deteriorated their SDS. Treatment was proposed to stop hearing progression (n = 4) or for hearing maintenance (n = 8). At the last magnetic resonance imaging (MRI) before surgery, the average VS size was 14.8 mm [7;23] in greater diameter along the IAC axis and 0.898 cm^3 [0.075;2.700] in volume. According to the Koos classification of VS extension, 4 presented as Koos 1 (intrameatal), 6 as Koos 2 (intrameatal and cerebellopontine angle), and 2 as Koos 3 (VS developed a close contact with the brainstem). Seven patients underwent the procedure on the only hearing ear. Five still had hearing in the other ear and the choice was guided to maintain binaural cues in younger children still at school (n = 3), or for hearing progression on both sides (n = 2).

Audiologic Findings

An early hearing response was observed in 3 of the 4 eligible patients during the first year following decompression.[12] A ceiling effect was present for the patients in the hearing maintenance group (8/12). Overall, SDS improved from 85% [20-100] to 92.5% [60-100] on average and more specifically from 55% [20-80] to 77.5% [50-100] in the hearing progression group (n = 4). These early results supported the hypothesis that a decompression could improve hearing in the first year after surgery (Table 2).

At long-term follow-up in the hearing progression group (n = 4), 2 patients still had hearing function on the side of the operated VS (swim graph, Figure 2). One with 90% SDS at 6 yr without other therapy. The other scored 24% at 4 yr after decompression and was therefore proposed further chemotherapy. The SDS improved at 94% 5 yr after starting bevacizumab therapy. One patient (1/4, hearing progression group) was fitted with a cochlear implant after a sudden hearing loss occurring 3 yr after decompression. In the hearing maintenance group (n = 8), one patient underwent a translabyrinthine craniotomy (TLC) 4 yr

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TABLE 2. Early Hearing Outcome

Case	Reference audiometry (PTA dbHL/SDS %/I-V ms)			Preoperative (PTA dbHL/SDS %/I-V ms)			Postoperative (PTA dbHL/SDS %/I-V ms)		
1	46.25	80	Absent	55	60	Absent	52.5	**100**	Absent
2	42.5	100	4.76	57.5	20	Absent	57.5	**50**	Absent
3	43.75	100	4.44	52.5	60	Absent	52.5	**100**	Absent
4	20	100	3.72	30	100	3.96	32.5	100	4.08
5	13.75	100	4	15	100	4.2	19	100	4.13
6	21.25	100	4.08	26.25	100	Absent	24	100	**5.16**
7	8.75	100	4.06	14	100	4.82	12,5	100	4.68
8	11.25	100	4.32	15	100	5.76	20	100	6.29
9	10	100	4.56	26.25	100	Absent	27.5	100	Absent
10	46.25	N/A	N/A	56.25	80	Absent	67.5	60	**4.28**
11	2.5	100	3.94	11	100	4.6	13	100	**4.41**
12	13.75	100	4.24	35	100	5.68	40	100	Absent

Best response during the first year after decompression "Reference Audiometry" refers to the historical audiometry obtained at the diagnosis of NF2 corresponding to the column "Preoperative Audiometric Follow-Up" from Table.

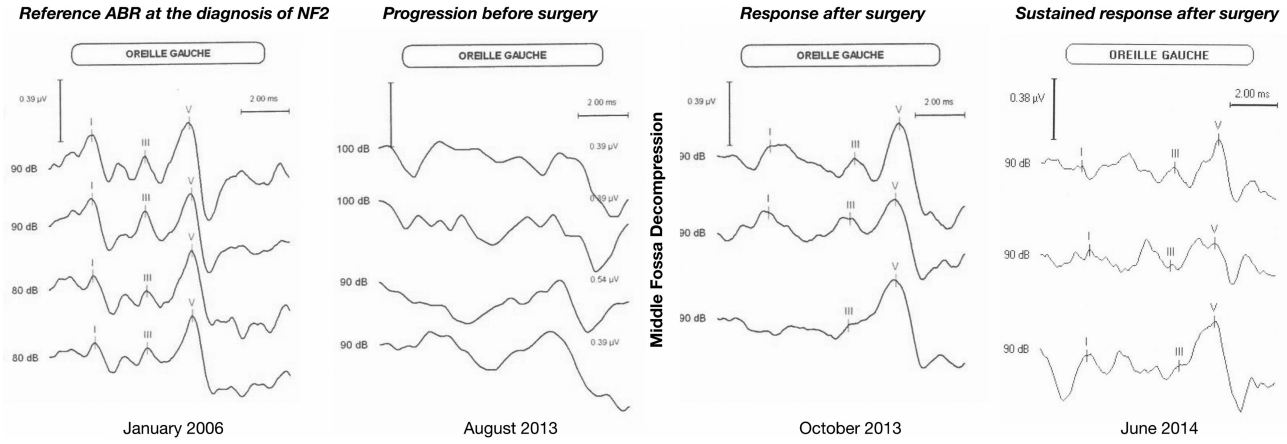


FIGURE 2. *Objective electrophysiologic hearing response. Modification of auditory brainstem responses across time, demonstrating a progressive improvement after decompression of the inner auditory canal.*

after decompression for continuous tumor growth at a growth rate of 0.397 cm^3/month before surgery, and hearing was maintained with 100% SDS until the TLC. One patient demonstrated an audiometric progression starting the third year following decompression. This progression was associated with a significant increase in volume. He therefore started bevacizumab during the fourth year following decompression. Unfortunately, no hearing response occurred under chemotherapy for this patient. At the last follow-up, 6 patients who were left without adjuvant surgery or chemotherapy reached an average SDS of 95.33% [84;100] at 3.16 [2;4] yr of follow-up. This observation is in accordance with previous reports that hearing may progress 2 yr after surgery. At the 3-yr follow-up, 6 patients had maintained 100% SDS.

Electrophysiology Assessment

In this study, we followed the patients' ABRs from the baseline status at the diagnosis of NF2. ABRs were then repeated during the follow-up period until the time of decompression. Overall, after decompression, the ABRs improved in 4 patients and were unchanged in 8 patients (Figure 1, Table 2). An example of ABR improvement is shown in Figure 2. Before decompression, 6 patients had reliable ABR, in which the wave III latency was 4.59 ms on average [3.85-5.52] and the wave V latency was 6.45 ms [5.66-7.44]. After decompression, the number of patients showing ABR increased to 9. The wave V latency was 6.44 ms [5.72-7.8], which was comparable to the preoperative mean latency even though at the individual level it was

TABLE 3. Hearing Response According to Cochlear Aperture Block

	Cochlear aperture block	Cochlear aperture free
Hearing response	5	1
No hearing response	2	4

A contingency table was built according to objective hearing responses and extension of the schwannoma to either of the cochlear apertures. Objective hearing responses are defined by either a significant increase in speech discrimination scores or significant reduction of wave III latency in auditory brainstem responses obtained at 90 dB SPL (odds ratio = 10 with a confidence interval of [0.64; 154.5]; Fisher's exact: *P* value = .24).

significantly shortened in 3 patients (Table 2, patients 6, 9, 10). Wave III became readable in 8 patients, and its latency decreased from 4.59 ms (n = 6) to 4.33 ms [3.96-5.4] (n = 8). These observations indicate that middle fossa decompression allows the effective release of a compressive neuropathy at the level of the eighth nerve because wave III is generated at the level of the cochlear nucleus.

VS on MR Scans and Extension

A senior radiologist (F.D.) who was blinded to the hearing outcomes reviewed all MR scans to confirm the degree of meatal filling. Extension to the fundus was defined according to the extension to the cochlear aperture. After building the contingency table (Table 3), we observed a beneficial advantage of the cochlear aperture block. The odds ratio for hearing response when there was a cochlear aperture block is 10 with a confidence interval range [0.64; 154.5]. The positive predictive value of hearing response in the presence of a cochlear aperture block is 83%. Though encouraging as a selection criteria, the difference between the groups did not reach significance (Fisher's exact, *P* value .24).

DISCUSSION

Limitations for Hearing Preservation Surgery

IAC decompression could be proposed as an alternative to removal surgery, knowing the many limitations to hearing preservation surgery. First, the tumor size must be considered in the choice of approach. In the literature, the average size for an MFC approach is 10 ± 0.4 mm.[13,14] Using this approach, the tumor size may limit the ability to save hearing and it was reported that 6 mm in greater diameter impaired hearing outcomes (average size of (0.9 ± 0.5) in the preservation group but (1.5 ± 0.6) in the group that lost hearing).[15] Overall, the results reported in larger NF2 cohorts suggested the hearing preservation rate was between 60%[13] and 50% for a useful hearing preservation rate, with 78% of these patients retaining good hearing at 2.8 yr.[14]

To improve the outcomes, several studies focused on the extension of VS to the lateral end of the IAC and stressed its association with decreased chances of hearing preservation during the removal of VS either through MFC or retrosigmoid craniotomy.[16-18] The extent of fundal involvement can be further specified. Indeed, VS may reach the fundus part of the CSF signal in T2 MR imaging, leave no CSF signal, extend to the cochlear aperture (ie, cochlear fossa for some authors), or pass through the cochlear or vestibular aperture. These findings have all been associated with worse hearing outcomes.[17,19] Since hearing maintenance is crucial in NF2, we elected to contraindicate the removal of the VS when it extended in the cochlear aperture on a preoperative MR scan.[16,19] Interestingly, the results reported herein suggest that the extension of a VS to the cochlear aperture may well benefit from decompression. Altogether, these results shed light on the importance of fundal evaluation and support using a technique of deep canal decompression that extends as close as possible to the lateral end of the IAC. In our experience, this can best be achieved via the systematic identification of the Bill's bar and blue lining of the superior semicircular canal.

Hearing Response and Mechanism of Hearing Loss

The mechanical compression and stretching of the cochlear nerve against the IAC wall could participate in hearing decline. Indeed, the bony IAC wall itself is subject to changes secondary to tumor growth.[20] Tumor growth within the IAC may alter hearing secondary to a compromised vasculature[21] or to an altered nerve to the tumor interface in NF2.[22] Although this hypothesis may not solely reflect the complexity of the mechanisms involved, the reported improvement in the ABR in some patients suggests that decompression could relieve such neuropathy. An entrapment syndrome within the IAC could explain part of this neuropathy. Follow-up of ABR responses could aid in the early identification of such an entrapment syndrome within the IAC and could therefore lead to proposing this surgery at an early stage when the neuropathy is still reversible.

Multiple changes affect the cochlea as well and contribute to hearing decline in VS patients. Among those, the block of the cochlear aperture may lead to increased intralabyrinthine protein levels. This is responsible for the changes in labyrinthine signals visible in fluid attenuated inversion recovery (FLAIR)-weighted imaging.[23] The protein content of the perilymph in VS patients is elevated at a concentration ranging from 4.6 to 30 μg/μL when control sampling at approximately 2 μg/μL.[24-26] "It has been reported that there is a high sensitivity of such elevated protein content in hearing loss ears in NF2 (94%) and a high negative predictive value of normal protein content in identifying normal hearing ears (91%)".[23] However, in the same study, an elevated protein level was reported in many of the normal hearing ears (35 of 47). In non-NF2 patients, intracochlear signal intensity has been shown to be related to hearing levels.[27] Recent studies of perilymph and CSF content identified some biomarkers of interest, "among which only 1 of the proteins was differentially expressed in VS with class D hearing (fibronectin 1) overlapping with the candidate perilymph and tumor secretion proteins."[28] The full mechanism by which increased protein levels affect hearing is not fully understood. Consequently, we hypothesize that IAC

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decompression could help in maintaining better homeostasis in the perilymph by relieving the block at the cochlear aperture and restoring protein exchange between the CSF and perilymph across the porus canaliculi within the modiolus.[29] Elevated protein levels may develop as a result of extracellular vesicles released by tumor cells.[30] Therefore, a limitation of our study was the lack of 3D-FLAIR MRI imaging pre- and postoperatively to investigate the possible changes in the intralabyrinthine protein levels. This imaging assessment in combination with electrophysiology, including electrocochleography with recording of microphonic potential, would help determine the critical underlying mechanism of hearing responses. In our study, we report on the early hearing responses following IAC decompression surgery. A better understanding of the mechanisms of hearing loss in VS patients is needed to prolong this response because the expected period of hearing maintenance is 2.1 yr after surgery, according to Slattery et al.[5]

Medical Treatment

Medical therapy for the treatment of VS occurring in NF2 has been reported. Until now, bevacizumab is the only compound that has demonstrated some effect on improving hearing.[7,8] Hearing response is observed in up to 57% of patients who are eligible for hearing comparisons. Therefore, it has been popularized and used by many teams. Given this prospect, the legitimate place of IAC decompression must be reset and balanced with the alternative of medical therapy. Meanwhile, the use of bevacizumab in these patients is off-label in many countries, and the cost might be an issue either for patients or for institutions. Regardless, considering the outcomes reported in this study, IAC decompression could lead to hearing improvement. Therefore, one should consider both approaches and coordinate these treatments after a multidisciplinary assessment. It remains to be determined whether a combined approach could have an additive effect and whether medical therapy should be added immediately or sequentially in hearing-compromised patients. A targeted partial removal under continuous hearing monitoring could also be considered since this approach led to the high hearing preservation rates reported in early work by Wigand et al.[31] Considering the overall safety in all series of IAC decompression, it is reasonable to think that one should consider a surgical approach first and a potentially lifelong chemotherapy second.

Asymmetric Hearing Loss

Asymmetric hearing loss (AHL) results in altered quality of life in adults and children.[32] It also exposes children to higher rates of grade failures at school when compared to their normal hearing pairs.[33-35] The audiologic definition for AHL includes any PTA difference greater than 10 to 15 dB hearing level.[36] This definition does not take into account the discrepancy observed in retrocochlear disorders in which speech is more altered than pure tone, nor for lateral specialization such as the right ear advantage.[37] In our study, we included first-sided progressive hearing loss in children and young adults since the proposed technique is conservative and has been shown to be safe.[6] Actual therapies focus on maintaining hearing but mostly unilaterally. We consider that in dedicated cases maintaining binaural hearing is crucial. An increasing literature on the benefit of maintaining binaural hearing even with signal as altered as those proposed by a cochlear implant (bimodal hearing rehabilitation) is beneficial in many aspect of life.[38] There is little consensus on the required magnitude of improvement of SDS to restore binaural abilities. As for any other condition leading to single-sided deafness (SSD), the evaluation of binaural benefit requires the use of hearing in noise and localization tests.[39] Such assessment has not yet been used in NF2. There is therefore limited knowledge of the true consequence of AHL/SSD in NF2.

CONCLUSION

Objective hearing responses could be obtained secondary to the decompression of the IAC through an MFC approach. This improvement may not last after 2 yr of follow-up. Larger multicenter studies could help further delineate the best timing for such surgery, in light of the potential benefits of bevacizumab chemotherapy. Preoperative assessment should include SDS, ABRs, and intralabyrinthine FLAIR-MRI to precisely determine the most likely mechanism of hearing progression. Patients should be informed of the expected period of hearing maintenance with this technique.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Internal auditory canal decompression through a middle fossa craniotomy is more and more often discussed among the therapeutic options for hearing maintenance, especially by the otoneurosurgical teams of specialized NF2 centers. This intervention is a useful procedure for hearing maintenance in NF2 patients, with very low morbidity for facial and hearing, as we reported previously in *Neurosurgery*.[1] In the current paper, the authors report an excellent hearing preservation rate and, in addition, some cases with hearing improvement. A remarkable element is that the authors have followed the patients' auditory brainstem responses (ABR) from the baseline status at the diagnosis of NF2. ABR were then repeated during the follow-up period until the time of decompression. Overall, after decompression, the ABRs improved in 4 patients. This is exactly the way we also follow patients in our NF2 reference center and we believe it should be done more often knowing that the EABR are often desynchronized or absent even with a good hearing level.

It is difficult for the moment to choose when facing hearing deterioration with vestibular schwannoma between decompression or Bevacizumab and this choice largely depends on the center where patients are followed and treated. In our center, we favor Bevacizumab for growing tumors with declining hearing. We offer internal auditory canal decompression in case of fluctuating or declining hearing, considering progressive alteration of EABR as hearing worsening. In addition, there are anatomical considerations on the vestibular schwannoma localization (ideally not restricted to the fundus without cochlea penetration but filling the internal auditory canal) and petrous bone anatomy. If despite internal auditory canal decompression the hearing continues to degrade, Bevacizumab has its entire place even without tumor growth.

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1. Bernardeschi D, Peyre M, Collin M, et al. Internal auditory canal decompression for hearing maintenance in neurofibromatosis type 2 patients. *Neurosurgery*. 2016;79(3):370-377.

This is an intriguing and well-written report regarding the advisability of internal auditory canal (IAC) decompression in patients with NF2 associated vestibular schwannomas (VS). The authors operated

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on 12 selected patients among 110 NF2 patients that they follow in their clinic. The indication for surgery was progressive hearing decline in 4 patients and a decline in the auditory brainstem response (ABR) in all patients. There were no surgical complications, reinforcing previous reports indicating this technique is at least safe. One of the difficult issues that have led us to be reluctant to enthusiastically adopt this practice is: There is no way to have a control group. Hearing in a patient with NF-2 is notoriously unpredictable. We often see the larger tumor is associated with the better hearing ear for instance? Additionally, we have seen patients with rather aggressively growing tumors have excellent, stable, hearing and other patients develop sudden severe hearing loss with no radiographic change in a small tumor.

Of course, as acknowledged by the authors, there may be many causes of hearing loss in patients with VS, and NF2-associated VS in particular, including direct compression of the cochlear nerve by the tumor leading to demyelination and axon loss, vascular comprise of the nerve or inner ear, direct invasion of the inner ear by tumor or alteration of the perilymph composition with deposition of protein in the cochlea to name a few of the most commonly suggested mechanisms. The improvement of the ABR is compelling evidence that in some patients it is indeed just a compressive neuropathy that may be driving the progressive hearing loss. I think this study also provides more convincing evidence that NF2 patients should be followed with serial ABRs in addition to the standard audiogram and MRI scanning. Although, it is equally notable that some of the best results in this study (patients 1 and 3 or example) had absent ABRs in follow-up.

It should also be mentioned, a speech discrimination score (SDS) improvement from 85% to 92.5% may indeed not be truly significant and likely falls within the test/retest variability of a standard audiogram but the improvement in SDS in the patients who presented with declining hearing from 55% to 77.5% is very notable.

An intriguing question raised by one of the hearing progression patients that was subsequently "rescued" with bevacizumab is: Could there be a synergistic effect from IAC decompression and bevacizumab? In a disease in which prospective studies are hard to do, this may be a worthwhile and achievable undertaking to randomize patients who are candidates for bevacizumab (progressive tumor growth on serial MRI or hearing decline or both) to drug alone vs IAC decompression and drug.

At the very least, this small series helps possibly identify a subset of patients that might be considered for IAC decompression. In particular, considering IAC decompression for NF2 patients with tumor extension to the cochlear aperture and have an abnormal ABR, especially prolongation of the Wave III-V latency or a poorly reproducible Wave III? However, whether this strategy really results in a long duration of hearing preservation is still not clear as only 50% of patients whose hearing was declining at the time of decompression maintained useful hearing at last follow-up? For most NF-2 patients likely any hearing for any duration is better than the alternative.

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Intraneural IFG-1 in Cryopreserved Nerve Isografts Increase Neural Regeneration and Functional Recovery in the Rat Sciatic Nerve

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Received, December 13, 2017.
Accepted, June 25, 2018.
Published Online, July 27, 2018.

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BACKGROUND: Insulin-like growth factor 1 (IGF-1) was found to stimulate Schwann cell mitosis. Exogenous IGF-1 may improve nerve regeneration after cryopreservation.

OBJECTIVE: To evaulate the effect of intraneural administration of IGF-1 in cryopreserved nerve isografts.

METHODS: Eighteen millimeter grafts were used for bridging an 18-mm defect in the rat sciatic nerve. A total of 57 rats were randomly divided into three groups: (1) autograft (Group 1); (2) cryopreserved isograft (Group 2); (3) cryopreserved isograft with intraneural IGF-1 administration (Group 3). 12 weeks after surgery, functional recovery (Sciatic functional index [SFI], Swing speed [SS], nerve conduction velocity [NCV], amplitude of compound motor action potentials [CMAP], and gastrocnemius muscle index [GMI]) and nerve regeneration (myelin sheath area, total fiber counts, fiber density, and fiber width) were all evaluated.

RESULTS: The intraneural injection of IGF-1 significantly improved SFI and SS at weeks 10 and 12. There were no statistical differences between Groups 1 and 3 in any of the SFI or SS evaluations. CMAP and NCV in Group 1 were significantly higher than in Groups 2 and 3, and Group 3 had significantly higher CMAP and NCV compared to Group 2. No significant differences were found in fiber width. The number of nerve fibers, percentage of myelinated fibers, fiber density, and GMI was significantly higher in Group 1 compared to Group 2, but no significant differences were found between Groups 1 and 3.

CONCLUSION: The results show that intraneural injection of IGF-1 in an 18 mm cryopreserved isograft improve axonal regeneration and functional recovery.

KEY WORDS: Albumin, Cryopreservation, Insulin-like growth factor I, Peripheral nerves, Sciatic nerve, Tissue adhesions, Tissue transplantation

Neurosurgery 85:423–431, 2019 DOI:10.1093/neuros/nyy339 www.neurosurgery-online.com

Despite the advances in microsurgery, the reconstruction of major defects in the peripheral nerve continues to be a challenge in clinical practice.[1,2] The optimal treatment for a peripheral nerve defect is the use of nerve grafts from the patient him or herself (autograft). Disadvantages of this technique include limited availability and iatrogenesis in the nerve graft donor area, consisting of anesthesia or local pain.[3,4] Among the alternatives to the autografts, the nerve allografts are indicated when major nerve defects are present and where autografts are insufficient.[5]

ABBREVIATIONS: CMAP, compound motor action potentials; **GMI,** gastrocnemius muscle index; **IGF-1,** insulin-like growth factor 1; **MNCV,** motor nerve conduction velocity; **NCV,** nerve conduction velocity; **SFI,** sciatic functional index; **SS,** swing speed

Cryopreservation is a method of conservation of tissues by means of cold treatment, which allows metabolic needs of tissues to be reduced to a minimum. Nerve cryopreservation is used to reduce immunogenicity within the graft, although maintaining viable Schwann cells and the scaffold for which Schwann cells can travel.[6,7] This technique also permits long-term storage of nerve tissue in tissue banks, and immediate availability of cryopreserved allografts. Immunosuppression is necessary to avoid rejection of the graft, although Squintani et al[8] reported the use of cryopreserved nerve

allografts in the clinical setting with no adjuvant immunosuppression.[9] The aim of the cryopreservation process is to keep Schwann cells viable, so that, theoretically, nerve regeneration will be greater than in acellular nerve grafts, which lack such cells.[10]

Apart from the scaffold for the regeneration of the nerve, we know that growth factors aid nerve regeneration.[11] Insulin-like growth factor 1 (IGF-1) is a growth factor which has been shown to stimulate Schwann cell mitosis, so that it should boost the regeneration of the cryopreserved isograft.[12] This growth factor improves nerve regeneration when administered locally on a daily basis or every other day.[13-15] Single intraneural dosing and evaluation of the local effects of this neurotrophic factor are needed.

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METHODS

Animals

The study was approved by the Institutional Review Board and all animal care complied with the Guide for the Care and Use of Laboratory Animals. Fifty-seven female adult Wistar-Lewis rats, (11-13 wk of age, weight 210-280 g) were randomized to 1 of the following groups: autograft (Group 1), cryopreserved isograft (Group 2), and cryopreserved isograft and intraneural IGF-1 (Group 3). Using the same strain of animal as donors would allow us to study the effects of cryopreservation over the nerve isograft, without interference of rejection.

In each of the three groups, 19 animals underwent sciatic nerve surgery. Nineteen rats were used as nerve isograft donors.

Inhalation anesthesia was applied, using sevoflurane. Surgery was performed under aseptic conditions using an operating microscope (Optomic OP-C12, Madrid, Spain).

Preparation of Cryopreserved Nerve Isografts

Nineteen rats underwent bilateral sciatic nerve surgery. Thirty-eight sciatic isografts were harvested. By means of a dorsal incision in both gluteal regions, biceps, and semitendinous muscles were exposed. After dissecting the sciatic nerve between these muscles, a 25-mm nerve graft was obtained and stored individually in sterile recipients in Medium 199 with 10% DMSO (dimethyl sulfoxide) and 4% human albumin. The cryopreservation process was performed using a cooling rate of 1°C per minute down to −140°C, the nerves being stored in nitrogen gas for 3 to 4 wk. Thawing was carried out at ambient temperature for 5 min and warm water bath for 10 min.[16]

Animal Experiment

Under inhalation anaesthesia, the rats were placed in a left lateral decubitus position. A longitudinal dorsal incision was made in the left gluteal area. An 18-mm length of sciatic nerve was removed at mid-thigh level and the nerve defect was repaired by (1) using the same autograft that has been resected in Group 1 (Auto), (2) using cryopreserved nerve isograft alone in Group 2 (Iso), or (3) using cryopreserved nerve isograft and intraneural IGF-1 injection in Group 3 (Iso-IGF1; see Figure 1, which illustrates a schematic representation of the 3 groups). All grafts were 18 mm in length, and the repair was tension-free, using 9-0 nylon suture at each end. In Group 3, the intraneural injection of recombinant human IGF-1, 25 μL (10 mg/ml, Increlex® 2 mg) was performed after the distal suture was made, at epineural level of the proximal graft, in order to preserve the fascicular nerve architecture, using a micropipette (Stripper® Tip, 135 μm, Origio, Denmark) through the proximal end of the graft.

Animals were monitored postoperatively for infection, pain, and distress. After the functional and histological assessment at 12 wk, rats were euthanized with intrapericardial injections of Potassium Chloride (2 mEq/ml, B. Braun, Aschaffenburg, Germany).

Sciatic Functional Index and Swing Speed

Sciatic functional index (SFI) and swing speed (SS) were taken before surgery (0 wk) and after 2, 4, 6, 8, 10, and 12 wk postoperatively, according to the method described by Westerga and Gramsbergen[17] and the formula proposed by Chen et al,[18] respectively. The video recording technique was performed as reported by Walker et al[19] and Dijkstra et al.[20]

The variables measured for the feet on the experimental (E) and normal side (N; expressed in milimeters) were as follows:

(1) Print length (PL): Distance between heel and toe.
(2) Toe spread (TS): Distance between first and fifth toes.
(3) Intermediary toe spread (IT): Distance between second and fourth toes.

SFI was calculated according to the method described by De Medinaceli,[21] using the modified formula described by Bain et al.[22]

$$\mathrm{SFI} = -38.3\left(\frac{EPL-NPL}{NPL}\right) + 109.5\left(\frac{ETS-NTS}{NTS}\right) + 13.3\left(\frac{EIT-NIT}{NIT}\right) - 8.8$$

In general terms, SFI values vary from 0 (normal nerve function) to −100 (absence of sciatic function).

SS is the speed at which limbs travel between steps, and it was calculated with a manually quantitative gait analysis method, dividing the distance of the step by the time of the swing phase. The relative SS was calculated as reported by Chen et al[18] as the ratio of the SS of the left hindlimb (experimental side, LSS) to the SS of the right hindlimb (normal side, RSS), and standarized against the baseline ratio (ratio of baseline SS of the left hindlimb, bLSS; to baseline SS of the right hindlimb, bRSS).

$$\mathrm{SS}\ (\%) = \frac{\frac{LSS}{RSS}}{\frac{bLSS}{bRSS}} \times 100$$

The theoretical values for relative SS vary from 0% (absence of sciatic function) to 100% (normal nerve function), being usually above 30% after sciatic nerve injury.

Neural Electrophysiology

The electrophysiological recording was determined as reported previously.[23] Twelve weeks following surgery, the electrophysiology study was performed using an amplifier (AM Systems, Jaen, Spain) connected to a Power 1401 interface (Cambridge Electronic Design Limited, Cambridge, United Kingdom), to measure the compound motor action potential (CMAP) and CMAP onset latencies. The registers were stored and processed using Spike 2 software (Centre d'Estudis Demogràfics, Barcelona, Spain), by an electrophysiologist, blinded to the method of treatment. Under inhalation anesthesia, surgical exposure of the grafted sciatic nerve was realized. Stimulating bipolar electrodes were placed both

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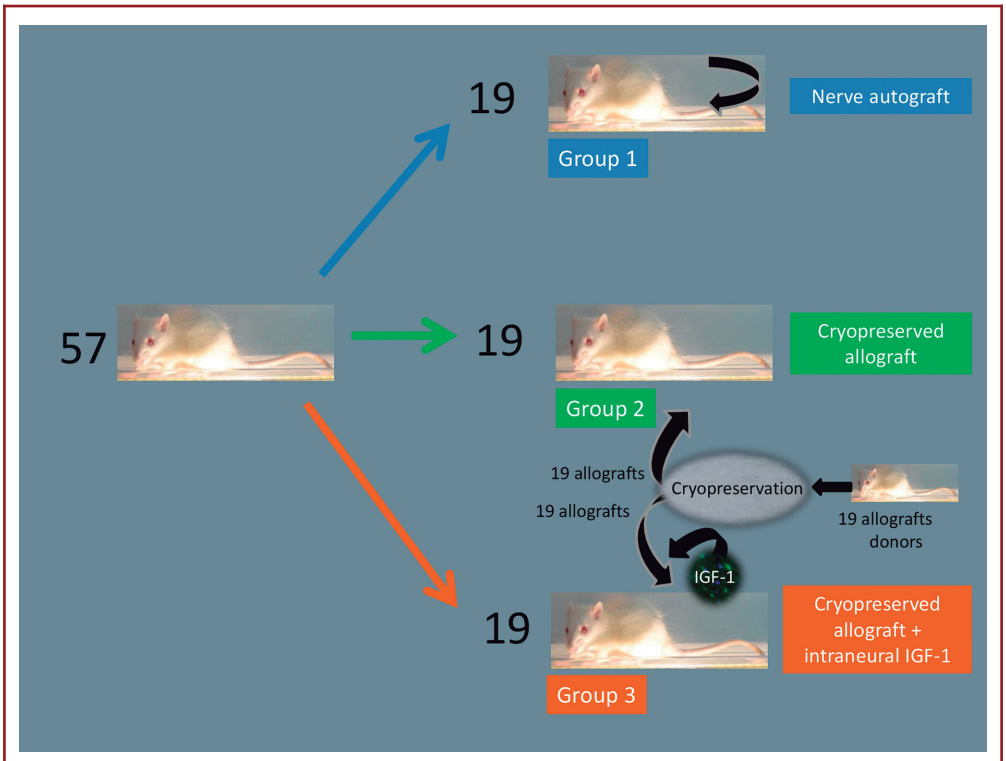


FIGURE 1. *Schematic representation of the groups designed in this study. In Group 1, the gap of the sciatic nerve was bridged with an autograft from the same rat. In Group 2, cryopreserved isografts were used to reconstruct the sciatic nerve defect. In Group 3, IGF-1 was injected into the cryopreserved isografts used to reconstruct the defect.*

proximal and distal to the graft, and the register electrode was placed in the gastrocnemius muscle. The distance between the bipolar electrodes was recorded. The difference of latencies between both registers was used to calculate the motor nerve conduction velocity (MNCV).

MNCV was calculated as follows:

$$\text{MNCV (m/s)} \frac{Distance\ between\ two\ points\ (m)}{\Delta latency\ between\ two\ points\ (s)}$$

Gastrocnemius Mass Index

After electrophysiology studies and histology nerve sampling were completed, gastrocnemius muscles from both the normal (right) and experimental (left) side were removed and weighted using an electronic balance with a precision of 1/10 000 g.

The gastrocnemius mass index (GMI) was calculated using the following formula:

$$\text{GMI (\%)} = \frac{Wet\ weight\ of\ the\ experimental\ side\ (left)}{Wet\ weight\ of\ the\ control\ side\ (right)} \times 100$$

Histological Analysis

After the electrophysiological studies were completed, 3-mm samples were taken proximal to the distal suture line for histological analysis. Fixation with 10% formalin was performed for 24 h, followed by gradient alcohol dehydration and paraffin inclusion. Cross-sections 4 μm in width were cut with a microtome. Deparaffinization of the slices was performed at 60°C with xylene. They were later hydrated by immersion in 100° alcohol, 96° alcohol and tap water, stained by Harris hematoxylin for 5 min, rinsed in tap water, incubated in eosin staining for 1 min, dehydrated in 96° alcohol and 100° alcohol and immersed in xylene. Eight hematoxylin and eosin stained slices per nerve were observed under light microscopy in order to observe inflammatory infiltrate and the general structure of the nerve. The presence and extension of perineural scar and hypervascularized tissue surrounding the graft were assessed by 2 blinded pathologists, through a semiquantitative scale.

Electronic Microscopy

Three-mm segments were harvested from both the distal graft and distal nerve, and fixed in 2.5% glutaraldehyde for 12 h at 4°C in 0.1 M cacodylate buffer with pH 7.4, followed by postfixation in 1% osmium tetroxide, gradient acetone dehydration, and inclusion in a SPURR low-viscosity epoxy resin. The segments were cut with the ultramicrotome in 60 nm slices, dyed with Toluidine Blue, and observed under a JEM 1010 transmission electron microscope (Jeol, Akishima, Japan). Images were taken with a Mega View III digital camera and analyzed by analysis software (Soft Imaging System GmbH, Olympus, Shinjuku, Japan). The thickness of the myelin sheath, the area of nerve fibers, the total number of nerve fibers, the percentage of myelinated nerve fibers, and the density of nerve fibers were all quantified in 10 random fields of vision, magnified 2000 times, in slices from the distal nerve fragment. The pathology technician was blinded to the method of treatment.

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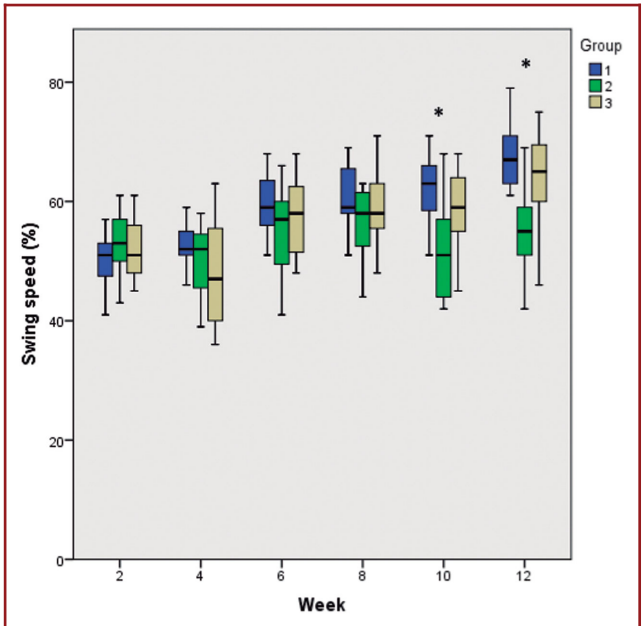


FIGURE 2. *Graph showing the evolution of SS in the 3 groups. *P < .05 compared to the autograft. There were no significant differences between groups until week 10. This could be explained because ten weeks is roughly the time frame expected for the regeneration front to reach the distal target. SS was superior in Group 1 compared with Groups 2 and 3 both in weeks 10 and 12. However, there are significant differences between Group 1 and Group 2 but not between Group 1 and Group 3. Group 3 significantly improved SS results in weeks 10 and 12 compared with Group 2.*

Statistical Analysis

A descriptive analysis was performed for all the variables included, expressing them as the mean ± SD (Standard Deviation), in addition to the 95% confidence interval. Statistical analysis was carried out with the nonparametric Kruskal–Wallis test. The Mann–Whitney *U* test was then used as a *post hoc* test. The correlations between the quantitative measurements were determined by means of the Spearman correlation coefficient. SPSS 22.0 software (IBM Inc, Armonk, New York) was used for analysis. $P < .05$ (<5%) was considered a significant difference.

RESULTS

Sciatic Functional Index and Swing Speed

During week 2, significant differences were found between the groups in SFI ($P = .04$), but not in SS ($P = .15$; see Figure 2 showing a schematic representation of SS). Group 2 SFI was significantly lower than that of Group 1 ($P = .04$) and Group 3 ($P = .01$), no differences being found between Groups 1 and 3 ($P = .66$). At 2 wk there is not enough time for reinnervation in a 18-mm graft, and the absence of significant differences in SS is more reliable than the results of SFI, which seem artefacted possibly because of the differences of the overall speed.

In the SFI of weeks 4, 6, and 8, no statistically significant differences were found ($P = .13$, $P = .06$, and $P = .08$ respectively), nor in the SS of weeks 4, 6, and 8 ($P = .21$, $P = .23$, and $P = .11$ respectively).

During weeks 10 and 12, statistically significant differences were found between the groups in the SFI ($P = .04$ and $P = .01$, respectively) and in the SS ($P < .001$ in both weeks). SFI was significantly greater in Group 1 compared with Group 2 ($P = .01$ in week 10, $P = .001$ in week 12), with no difference being found between Groups 1 and 3 ($P = .32$ in week 10, $P = .11$ in week 12), nor between Groups 2 and 3 ($P = .21$ in week 10, $P = .06$ in week 12). SS was also superior in Group 1 compared with Group 2 ($P < .001$ in both weeks 10 and 12), without significant difference between Groups 1 and 3 ($P = .12$ in week 10, $P = .079$ in week 12). SS in Group 3 was significantly greater compared with Group 2 ($P = .001$ in week 10, $P < .001$ in week 12).

Neural Electrophysiology

Statistically significant differences were found between the groups in CMAP ($P = .001$) and nerve conduction velocity (NCV) ($P = .001$), which were significantly higher in Group 1 than in Group 2 ($P = .001$ in CMAP, $P = .001$ in NVC) and Group 3 ($P = .005$ in CMAP, $P = .02$ in NVC), and higher in Group 3 compared with Group 2 ($P = .04$ in CMAP, $P = .04$ in NVC).

Gastrocnemius Mass Index

Statistically significant differences were found between the 3 groups in GMI ($P = .001$), significantly lower in Group 2 compared with Groups 1 and 3 ($P = .001$ between Groups 1 and 2, and $P = .001$ between Groups 2 and 3), no significant differences being found between Groups 1 and 3 ($P = .42$).

Hematoxylin and Eosin

Preservation of epineurium and perineurium was observed in all groups, as was the presence of neovessels. Unlike the nerve's appearance at the time of the surgical intervention, (see Figure 3, which illustrates the macroscopic nerve appearance after the neurorraphy), at 12 wk, epineural-mesoneural adhesions were observed macroscopically, being observed consistently in Group 2 of the cryopreserved isografts, and present, though to a much lesser extent, in Group 1 of the autografts.

However, in the cryopreserved isografts from Group 3, which had been injected with intraneural IGF-1, the isograft was found to be surrounded by shiny hypervascularized tissue, unattached to the surrounding muscle, permitting blunt dissection of the isograft. By using hematoxylin and eosin, it was found that this tissue was made up of subcutaneous fat, rich in numerous neovessels (see Figure 4 for further details), quite similar to the normal epineural-mesoneural tissue. The presence of perineural scarring was significantly superior in Group 2 than Group 1 ($P = .001$) and 3 ($P = .001$), and in Group 1 than Group 3 ($P = .021$; see Table 1 for further details). Hypervascularized tissue was significantly more frequent in Group 3 than Group 1 ($P < .001$) or Group 2 ($P < .001$), and in Group 1 than Group 2

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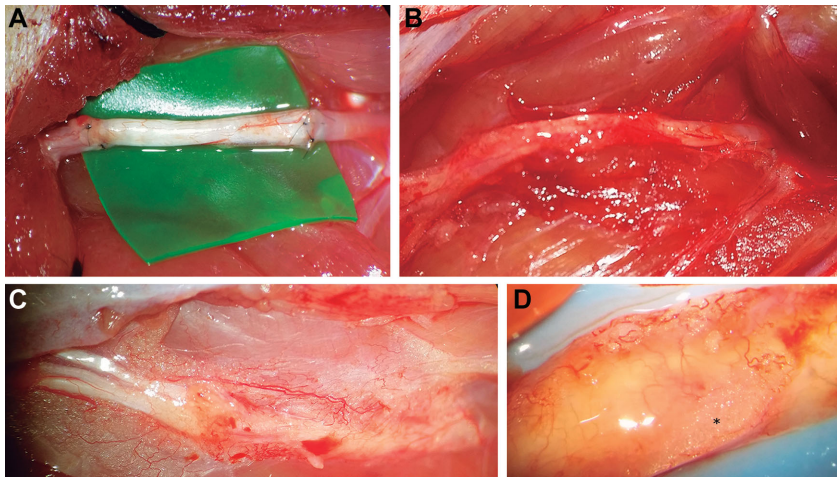


FIGURE 3. *Macroscopic view of the nerve grafts.* **A**, *View of sciatic nerve at time of neurorrhaphy of graft.* **B**, *View of the cryopreserved nerve isograft 12 wk after surgery. Note the scarred aspect of the nerve, attached to the underlying muscle bed.* **C**, *View of cryopreserved nerve isograft with IGF-1 12 wk after surgery, surrounded by the shiny loose epineural tissue (4×), and* **D**, *shows a detail of the epineural tissue (marked with a black asterisk; 40×).*

($P = .013$; see Table 2 for further detail). An inverse correlation between the presence of perineural scarring and hypervascularized tissue was found, meaning that the more hypervascularized tissue the lesser scarring ($R = -.708$, $P = .01$).

Electron Microscopy

At 12 wk, Groups 1 and 3 had a larger number of myelinated nerve fibers than Group 2 (see Figure 5, which illustrates the aspect of the nerves with electron microscopy).

Differences were observed between the 3 groups regarding the thickness of the myelin sheath ($P = .001$), which was significantly greater in Group 1 compared with Groups 2 ($P = .001$) and 3 ($P = .002$), no significant differences being observed between Groups 2 and 3 ($P = .15$).

No differences were found in the average area of nerve fibers ($P = .93$).

The number of regenerated nerve fibers and the percentage of myelinated nerve fibers in the distal nerve differed significantly between the groups ($P = .02$ and $P = .04$, respectively). In both cases, they were significantly higher in Group 1 compared with Group 2 ($P = .006$ and $P = .01$, respectively), but no statistically significant differences were observed either between Groups 1 and 3 ($P = .27$ in total number of nerve fibers and $P = .16$ in percentage of myelinated nerve fibers), or between Groups 2 and 3 ($P = .08$ in total number of nerve fibers and $P = .24$ in percentage of myelinated nerve fibers).

Statistically significant differences also existed between the groups in the density of nerve fibers ($P = .009$), which was significantly higher in Group 1 compared with Group 2 ($P = .002$), and in Group 3 compared with Group 2 ($P = .02$), without there being any difference between Groups 1 and 3 ($P = .41$).

DISCUSSION

In our experimental study, we observed that the intraneural injection of IGF-1 in the cryopreserved nerve isograft improved nerve regeneration and functional recovery, allowing similar results to those seen in the autograft group. Besides, in the group in which the growth factor was used, adipose tissue was observed around the nerve, which seems to prevent nerve scar adhesions to the surrounding muscle and reproduces the mesoneural tissue that surrounds the healthy nerve. Functional recovery parameters, such as SFI, SS, electrophysiology, and GMI, indicate significantly better results in the autograft when compared to the cryopreserved isograft. The addition of the growth factor means that outcomes improve, with the result that the cryopreserved isograft has functional recovery parameters similar to those of the autograft. In the histomorphometry, the density of nerve fibers was significantly superior when the growth factor was added. The improvement in the thickness of the myelin sheath, number of regenerated nerve fibers, and percentage of myelinated nerve fibers in the isograft with growth factor, although not statistically significant, demonstrates an enhanced nerve regeneration, similar to that of autograft.

As for nerve cryopreservation, there have been few experimental studies. The nerve cryopreservation has to be taken into account when the results obtained in our study are observed, since it constitutes the reason why Group 2 has worse results than Group 1 in regeneration and functional recovery. This is due to

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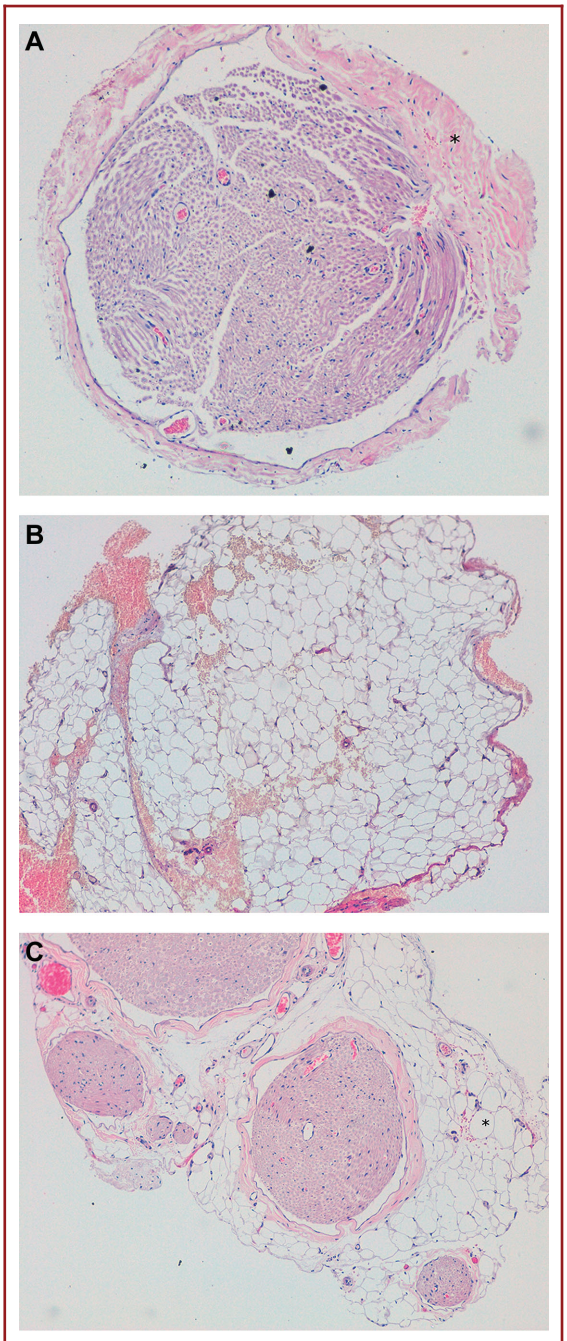


FIGURE 4. *Hematoxylin and eosin. 10×.* **A**, *Microscopic view of epineural scar (marked with a black asterisk) in a cross section of the cryopreserved isograft from Group 2.* **B**, *Microscopic view of epineural tissue surrounding the cryopreserved isograft with growth factor, consisting of mature adipose cells and blood vessels.* **C**, *Microscopic view of cross-section of normal sciatic nerve. Note the similarity of normal mesoneural tissue (***C**, *marked with a black asterisk) with the loose tissue reproduced around the cryopreserved isograft in the group with growth factor (***B**).

the fact that cryopreservation means eliminating the viablity of 25% to 40% of Schwann cells, and even though the graft scaffold and most of the cell population are preserved, this process involves repercussions when nerve regeneration and functional recovery take place.[6,7,10]

The protocol used in this study showed 74.9% of Schwann cell viability after cryopreservation, and a significant increase of viability when albumin is added to the cryopreservation protocol of the nerve grafts.[16]

As for the cryoprotectants used in nerve cryopreservation, Zalewski et al[9] established that the mixture of DMSO and formamide is superior to glycerol as a cryoprotectant for Schwann cells. Our group used DMSO and albumin in nerve cryopreservation, after greater viability was found when this protein was added to stabilize the membrane compared with using just DMSO. As for cooling and thawing rates, slow cooling and rapid thawing were used, as it has been shown that this method is that associated with greatest nerve fiber viability.[24]

The novel factor in this study was to introduce the use of IGF-1 in a single dose, administered at epineural level in the cryopreserved isograft.

IGF-1 presents a highly conserved structure among vertebrates, allowing the rat model to be suitable, even though the molecule of human IGF-1 is used.[25]

Neovessel formation is essential so that axonal regeneration can take place, and IGF-1 stimulates neoangiogenesis in nerve regeneration,[26,27] in addition to inducing the differentiation of non-adipocyte precursors to fat-filled mature adipocytes.[28] Along these lines and on the basis of the results of our study, we propose that the perineural adipose tissue observed in Group 3 could be related to the capacity of adipogenesis and neoangiogenesis of IGF-1. Further studies are necessary in order to find which precursors these adipocytes proceed from (satellite cells of muscle fibers, epineural or perineural cells), and which molecular mechanisms determine adipogenesis.

As for the perineural absence of adhesions which we found in Group 3, as far as we know, no publication has demonstrated this effect. As opposed to what we observed in the nerve scenario, IGF-1 has been related to the scarring of wounds, boosting neoangiogenesis, and local recruitment of macrophages.[29,30] In fact, the inhibition generated by glucocorticoids on the healing of wounds could be reversed by administering IGF-1.[31]

In order to find whether IGF-1 influences collagen formation locally, further studies would be necessary, with the aim of assessing the role of locally administered IGF-1 in perineural adhesions, an application which would be very interesting in relation to its use in clinical practice. We are unaware whether its local role varies according to the dose, nor the time its effect lasts.

Experimental evidence exists that IGF-1 stimulates peripheral nerve regeneration,[11,32,33] encouraging both growth in nerve length and nerve branching,[33–35] and also has a myogenic effect, stimulating proliferation and differentiation of myofibroblasts as well as muscle hypertrophy.[27,36-42]

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TABLE 1. Perineural Scarring

	Perineural scarring			
	0	+	++	+++
Autograft (Group 1)	47.4% (9/19)	47.4% (9/19)	5.2% (1/19)	0% (0/19)
Isograft (Group 2)	5.2% (1/19)	21.1% (4/19)	42.1% (8/19)	31.5% (6/19)
Isograft + IGF-1 (Group 3)	84.2% (16/19)	15.8% (3/19)	0% (0/19)	0% (0/19)
Total	45.6% (26/57)	28.1 (16/57)	15.8% (9/57)	10.5% (6/57)

Distribution of the rats of each group depending on the grade of perineural scarring showed in the histological analysis (0: no perineural scarring; +: mild perineural scarring; ++: moderate perineural scarring; +++: severe perineural scarring).
The percentage of rats is shown in each cell, while the number of rats in absolute figures is shown between brackets.
The table shows more intensity of the perineural scarring in Group 2, which was significantly superior than the scarring in Group 1 ($P = .001$) or 3 ($P = .001$). Group 1 had slightly more perineural scarring than Group 3 ($P = .021$).

TABLE 2. Perineural Hypervascularized Tissue

	Perineural hypervascularized tissue			
	0	+	++	+++
Autograft (Group 1)	52.6% (10/19)	36.8% (7/19)	5.3% (1/19)	5.3% (1/19)
Isograft (Group 2)	94.7% (18/19)	5.3% (1/19)	0% (0/19)	0% (0/19)
Isograft + IGF-1 (Group 3)	15.8% (3/19)	10.5% (2/19)	26.3% (5/19)	47.4% (9/19)
Total	54.4% (31/57)	17.6% (10/57)	10.5% (6/57)	17.5% (10/57)

Distribution of the rats of each group depending on the grade of perineural hypervascularized tissue showed in the histological analysis (0: no perineural hypervascularized tissue; +: mild perineural hypervascularized tissue; ++: moderate perineural hypervascularized tissue; +++: extensive perineural hypervascularized tissue).
The percentage of rats is shown in each cell, while the number of rats in absolute figures is shown between brackets.
The table reveals that the perineural hypervascularized tissue was more frequent and profuse in Group 3. The presence of hypervascularized tissue was significantly superior in Group 3 than Group 1 ($P < .001$) or Group 2 ($P < .001$). Group 1 had significantly more hypervascularized tissue than Group 2 surrounding the nerve grafts ($P = .013$).

IGF-1 has been studied in different models of lesions and nerve repair in rats. Mohammadi et al[43] found improved nerve regeneration when 10 μL of IGF-1 (100 ng/kg) was injected through an artery graft. Emel et a[44] found increased axonal regeneration when local repeated doses of 15 μg of IGF-1 were released over crushed sciatic nerve injuries in rats. In our study, the single dose administered when surgery was performed was of 25 μL (0.25 mg). In point of fact, one of the current limitations regarding IGF-1 is the absence of studies which examine the dose dependency of its effects. The maximum dose established for humans has been set at 0.012 mg/kg administered subcutaneously every 12 h, being only labeled to treat growth retardance due to deficits of IGF-1. In the current piece of work, a single dose was enough to boost nerve regeneration and functional recovery. We can only postulate that continuous administration by means of percutaneous pumps could improve results. However, when it comes to clinical practice, research into the role of single intraneural administration is appealing as it is much more feasible in daily practice.

In our study, we decided to sacrifice all the rats at 12 wk, in order to avoid an increase in subgroups and the possible alpha error which could be made. The "blow-through" effect described by Brenner et al[45] might determine that 4 or 8 wk after the surgical intervention there were greater differences between the groups. Nevertheless, we consider that the existence of significant differences at 12 wk is no justification for the sacrifice of more rats in order to study nerve regeneration 4 or 8 wk postsurgery.

The rats used in our protocol had the same haplotype, so the nerve isografts did not generate immune rejection and in our model it was unnecessary to use immunosuppression.[46] This model's design was conceived exclusively to study the role of nerve cryopreservation and the addition of IGF-1 in isolation, the results being unaltered by any contribution from the immune system.

Lastly, we believe that the potential clinical applicability of IGF-1 in peripheral nerve lesions in humans needs to be grounded in fresh experimental studies which would explore its neoangiogenic and anti-scarring properties, and which could provide us with another tool with which to undertake reconstructive peripheral nerve surgery.

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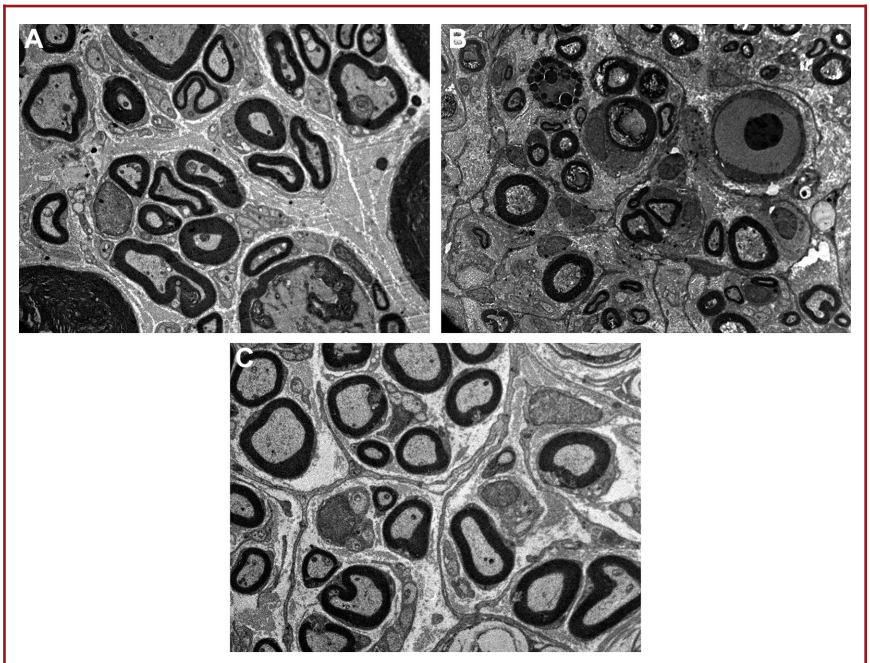


FIGURE 5. *Transmission electron microscopy. Cross section of the nerve grafts (2500×).* **A**, *Corresponds to a cross section of the autograft (Group 1) in its distal portion, showing good remyelinization, limited myelin debris, a large number of axons and similar width in nerve fibers.* **B**, *Corresponds to a cross section of the cryopreserved isograft (Group 2) in its distal portion. Note the irregular remyelinization, a large amount of myelin debris and great variation in the width of the regenerated nerve fibers.* **C**, *Corresponds to a cross section of the cryopreserved isograft with intraneural IGF-1 (Group 3) in its distal portion. The grafts with intraneural growth factor revealed more regular remyelinization, less myelin debris, and more uniform width in the myelin sheath and regenerated nerve fibers than those in the grafts from Group 2.*

CONCLUSION

This experimental study has shown that the application of a single dose of IGF-1 epineurally at the proximal end of the cryopreserved isograft improved functional recovery and sciatic nerve regeneration in the Wistar–Lewis rat model. Besides, the growth factor significantly increased epineural adipogenesis and prevented scar adhesions in the surgical bed.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We would like to thank Alan Floyd for the review of the manuscript transcription, Catalina Sueiro and Ada Castro for their major support in the assessment of the electronic microscopy images, and Jorge Pombo Otero, Ana Teijo, and Ana Reguero for their invaluable assistance in the interpretation of the histological images.

Greening the Operating Room: Results of a Scalable Initiative to Reduce Waste and Recover Supply Costs

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Received, November 23, 2017.
Accepted, July 10, 2018.
Published Online, July 27, 2018.

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Operating rooms generate 42% of a hospital's revenue and 30% of hospital waste. Supply costs are 56% of a total operating room (OR) budget. US academic medical centers use 2 million pounds ($15 million) of recoverable medical supplies annually. Forming a multidisciplinary leadership team, we analyzed sources of waste focusing on our Department of Neurosurgery. We developed an 8-wk pilot project to recycle "blue wrap," the number 5 plastic polypropylene material that is ubiquitously used in ORs across the country to wrap instrument pans and implant trays for sterilization. Blue wrap can be baled and sold to recyclers where the material is pelletized and transformed into plastic products. During the 39 d of the pilot, we collected 1247 pounds of blue wrap (32 lbs collected daily). The cost of the pilot was $14 987 that includes a new baler ($11 200) and 5 transport carts ($3697). The revenue received from baled blue wrap was 8 cents per pound. Cost avoidance yielded $31 680.00 in savings. Implementation of this pilot across our main hospital would yield $5000 in revenue annually and $174 240 in cost avoidance. This project can be replicated at other centers and not only reduces the environmental footprint, but also helps generate additional revenue by recycling a necessary packing material that would otherwise require payment for disposal.

KEY WORDS: Sustainability, Efficiency, Cost-effectiveness

Neurosurgery 85:432–437, 2019 DOI:10.1093/neuros/nyy275 www.neurosurgery-online.com

Surgeons have an opportunity to serve as leaders and stewards of resources, especially operating room (OR) supplies. Engaging in resource stewardship provides an important pathway through which physicians can champion waste reduction and employ environmentally sound and cost conscientious decision-making. Additionally, this provides another avenue to demonstrate leadership to administration and nurse managers typically involved in decision making of OR policy, for example.

Estimates suggest that between 20% and 70% of health care waste originates from a hospital's OR, and up to 90% of OR waste is improperly sorted and sent for costly and unneeded biohazardous waste processing.[1] Operating rooms generate 42% of a hospital's revenue and 30% of hospital waste.[2,3] Supply costs are 56% of a total OR budget.[4] One surgery alone may produce more waste than a family of 4 would create in 1 wk.[5-8] US academic medical centers use 2 million pounds ($15 million) of recoverable medical supplies that can be reused through sterilization or processing, annually.[9-11]

As much as 80% of solid waste for an operation may be generated before a patient enters the OR.[12] A significant source of waste is plastic packaging, with many surgical products packaged in large containers and double-wrapped polypropylene plastic utilized to cover surgical instruments and maintain sterility during storage (Figure). This "blue wrap" contributes up to 19% of the total waste from ORs and creates significant disposal costs.[13] According to the University of Minnesota Medical Center, blue wrap is estimated to account for 19% of OR waste and 5% of all hospital waste.[14] Blue wrap is not biodegradable, but can be melted and recycled due to its polypropelene composition.[13]

Although some institutions have replaced blue sterile wrap with reusable rigid containers, blue wrap will likely always have a place in the OR.

ABBREVIATIONS: OR, operating room

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FIGURE. *Blue wrap in the OR. Image courtesy of the senior author.*

Containers can be more expensive and take up space, and some smaller items necessitate the use of blue wrap.

For example, our institution alone uses 67 600 pounds of blue wrap a year. From January 1 through March of 2017, our institution spent $54 321.34 on blue wrap.

Neurosurgeons face increasing pressures within hospitals to be responsible for cost cutting, OR efficiency, and for stewardship of resources. Leading OR initiatives to analyze and address resource use, waste, and recycling efforts places neurosurgeons in the driver seat, as opposed to passive recipients of practice change by administrators and those not engaged in patient care. For example, the senior author has had to change the type of sterile gloves he wears 7 times in the past 20 yr because nursing administration discovered "better cost effective alternatives," with no input from the operating staff. If physicians take the lead in initiatives such as this, we feel it is more likely we will maintain a "seat at the table" when additional measures are discussed in the future. Also, we believe neurosurgeons are seen as decisive leaders within the medical staff, and this role can be used to lead initiatives to address resource use and waste, which is increasingly important for hospital leadership and the public.

Given the number of surgeons who utilize multiple sterile covered instrument and implant pans, such as for instrumented spine operations, and the need for sterile "blue wrap" around most sterile instrument pans and implant trays, we present a pilot study of redesigning a waste management stream to collect, bale, and sell blue wrap as part of our greening the OR initiative.

METHODS

Facility

The hospital site for the study is a 1265 bed facility with 55 ORs, and is a Level I Trauma Center with an academic affiliation. The neurosurgical department performs approximately 5000 surgical procedures yearly necessitating sterilized equipment. The department consists of 17 operating faculty, 21 residents, and 10 starting ORs per week day. The institution as a whole completes approximately 62 000 surgical procedures per year at 2 main hospital campuses and an outpatient surgery center.

Team

Interest in greening efforts in the OR occurred concurrently as the initiative was launched in collaboration between the primary author and several leaders within Waste Management and Recycling. Forming a multidisciplinary leadership team consisting of 2 leaders from Neurosurgery, 3 leaders from Waste Management and Recycling, 4 administrative leaders in Operating Room Nursing, 2 leaders in Anesthesia, 1 leader in Environmental Services, and 2 administrators from the Operating Room, we analyzed sources of waste and waste reduction steps we could implement at our institution focusing on the Department of Neurologic Surgery, which includes Orthopedic Spine surgery.

Project Selection

There were 3 meetings between Neurosurgery and Waste Management and Recycling leadership, and monthly or bimonthly meetings of the larger leadership team prior to launch. Formulation of the action plan occurred over a period of 6 mo, with discussions preceding this occurring intermittently for 2 yr. The strategy group held a brainstorming session and solicited feedback from individual neurosurgical residents and faculty, OR circulating nurses, scrub technicians, and surgical assistants as to targets for waste reduction. The strategy group also discussed single-use devices, supply packaging, electricity consumption, water usage, and biohazard bag volume. The ability to make a meaningful impact in cost containment and waste reduction, as well as the ease of implementation was discussed by the strategy group. Initiative ideas were scored based upon opportunity for impact, cost containment, ease of implementation, ability to track performance metrics, colleague buy-in/support, and the ability to advance the hospital's values. After weighing and ranking the initiatives with these criteria in mind, we chose to focus on collecting and recycling blue wrap as a first project.

Assessment

In terms of assessment, costs for training were allocated as a portion of personnel salaries for the individuals providing training. Trainings were delivered during regularly scheduled in-service educational periods, and did not require off-site travel or overtime pay for attendees. The estimated costs for training were $1000. Since the trainers were waste management staff who had responsibilities to train OR staff on recycling processes and since the trainings were done during in-service periods, this was not a direct cost upon the pilot. Costs associated with transport carts, blue wrap

receptacles, and waste management personnel to segregate the blue wrap receptacle from regular waste were calculated. We monitored compliance with the pilot through direct observation by the study authors. The study authors visited each OR 1 to 2 times per case to assess whether blue wrap was appropriately collected and placed in the correct receptacle. Determination for the ease of adoption was based upon formal feedback from OR circulating nurses, scrub technicians, and waste management personnel. A survey was employed to assess the average additional time required by OR staff to separately collect and deposit blue wrap into receptacles. We tracked the amount of blue wrap captured, by weight. We calculated cost savings by determining the revenue received from the sale of recycled pellets and deducting from this the costs associated with training and program implementation. We assessed environmental impact by evaluating cost avoidance, that is, the costs associated with disposal of trash, incineration, transport, and landfill usage. We also calculated the amount of energy saved from not having to destroy blue wrap waste.

Analysis

We launched an 8-wk (April 17, 2017-June 30, 2017) pilot program in the Department of Neurologic Surgery to collect all blue wrap used to cover sterile pans. Prior to the launch, we engaged in 4 OR staff, resident, and faculty 1-h training sessions. We used basic analytics and STATA SE15 statistical software (StataCorp LLC, College Station, Texas) to compile descriptive data on the collection and recycling efforts for the blue wrap.

RESULTS

Scoring of Potential Projects

We utilized the following parameters on a scale of 1 to 5, with 5 being most favorable and 1 being least favorable: opportunity for impact, cost containment, ease of implementation, ability to track performance metrics, colleague buy-in/support, and the ability to advance the hospital's values. After a brainstorming session to generate a list of ideas for waste reduction projects, we rank ordered the groups scores by project. Blue wrap, recycling hard plastic anesthesia disposables, and changing hand-washing agents to safer products with less environmental toxicity were the top 3 project ideas in rank order.

Costs

The cost of the pilot was $14 987 that included a new baler ($11 200) and 5 transport carts ($3697). The revenue received from baled blue wrap was net 8 cents per pound.

Cost Savings

Cost avoidance, meaning the costs associated with transport and waste disposal that would have otherwise occurred if the blue wrap were not recycled, yielded $31 680 in savings. Disposal of hazardous waste varies by municipality, but assuming a cost of disposal $25 per pound, with a $25 disposal charge, and $48 per hour for labor assuming 10 h of labor, the cost avoidance for disposal of blue wrap is $31 680.[15] In 2017, the institution spent approximately $217 285.36 on blue wrap and uses approximately 67 600 lbs of blue wrap annually. The initial investment for a site wide roll-out is approximately $22 000 in anticipated direct costs.

Revenue Generated

We project that adopting the pilot program across the institution after recouping costs associated with the initial investment would yield $5000 in revenue annually and $174 240 in cost avoidance related to decreased disposal and transport costs.

Calculated Environmental Impact

In the 39 working days of the pilot, with an average of 10 ORs/day, we collected 1247 lbs, of blue wrap which translates into 32 lbs collected per day. Assuming 40 lbs per cubic feet for disposal landfill area, the amount of landfill space saved is 31.2 cubic feet from our pilot. If this program were rolled out to impact OR suites across our institution at an 80% blue wrap recovery rate, we project 18 837.5 gallons of oil saved that translates into 158, 785 kWH of energy saved (Table).[16,17] The projected landfill space saved from roll-out is projected to be shy of filling a 26-foot moving truck.

Deficiencies/Obstacles for Implementation

We anticipate that the collection of blue wrap absorbed 2 to 5 min of additional time per room circulator per case, who would need to ensure that the collection receptacle was present, and that blue wrap was appropriately deposited into the collection bag. Over time, as OR staff become more comfortable with the processes, we anticipate this will be an average of 2 additional minutes per room circulator per case. Assuming an OR can cost $15 per minute, the range of expense during the pilot was $30 to $75 per case in the cost of additional OR time.[7] For the duration of the 39-d pilot, case volume was not adversely impacted, thus, the additional time cost of learning a new recycling process was assumed to be part of fixed overhead. With broader roll-out of the pilot, the financial cost of additional recycling processes, even if only 2 min on the average, may increase OR overhead expense. Feedback from OR and waste management personnel was acquired continually through the pilot as well as formally at the completion of the pilot. Initial feedback was related to personnel becoming familiar with the new workflow for blue wrap. At the completion of the pilot, OR nurses, scrub technicians, and waste management personnel provided feedback; 15 of 35 individuals queried responded and 90% were favorable towards the viability of the program and voiced support for ongoing participation with the program. 75% of respondents expressed enthusiasm for the institution's involvement in waste management recycling efforts.

Program Assessment

During the pilot period, all 10 ORs participated in the pilot program each weekday and this was monitored by one of the study authors (compliance = 100%). The weekends included 2 emergency ORs; blue wrap was collected for disposal the following Monday.

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TABLE. Municipal Waste and Savings; Projections for Full Roll-Out and Data From Pilot

	Pounds of waste collected	Space savings	Oil savings	Electricity savings
Pilot	1247 lbs.	31.2 cubic feet	376.75 gallons	3175.7 kWH
Projections for full roll-out	54 081.6 lbs.	1353.39 cubic feet	18 837.5 gallons	158 785 kWH

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DISCUSSION

Institutions have engaged in "Green OR" initiatives with tremendous results. For instance, one hospital system recycled 6.5 tons of medical waste over 5 yr, saved $50 000 per year by utilizing recyclable equipment instead of single-use devices, donated or distributed 500 pounds of previously discarded batteries (yielding $9000 a year in savings), would shut down anesthesia and OR lights and equipment when not in use, which saved $33 000 and 234.3 metric tons of CO_2 emissions per year, and used waterless scrub which saved 2.7 million liters of water per year.[18]

Surgeons are often encouraged to be stewards of resources within the hospital, particularly as it relates to limiting OR waste and consolidating resources to reduce cost. However, surgeons are rarely involved in recycling initiatives or minimizing an organizations' environmental footprint. Surgeons are uniquely poised to be leaders, shepherding these efforts and bringing together stakeholders around common goals. Surgeon to surgeon education can increase buy-in for recycling and greening efforts while education by nonpeers may be less effective.

In our paper, we present data from a pilot project to reduce the environmental impact of the waste of sterile blue wrap, necessary to properly cover instrument and implant pans during poststerilization storage. Our study bolsters other literature that has described greening efforts among surgical subspecialties. For instance, one study of orthopedic greening efforts found that an opportunity for waste reduction was in the successful reprocessing and reuse of external fixators, shavers, blades, burs, and tourniquets.[1] An orthopedic surgical study found that with staff education it was possible to reduce the amount of clinical waste generated by the OR by roughly 50%.[19] Another study found that downsizing the number of items in a disposable pack, from 15 to 7, yielded an annual cost savings of $17 381.05.[14] Single-stream recycling efforts in another study saved, on average, $3487 per month at 3 campuses, yielding a $41 844 savings per year.[14] It has been estimated that total knee replacements in Canada in 2008 to 2009 yielded the equivalent of 2000 garbage trucks of landfill waste.[20]

Recycling has increased in popularity in the United States; 34.7% of all waste was successfully recycled in 2011, which marks an increase from 16% in 1990 and 28.5% in 2000.[14] This interest in the environment and limiting the waste footprint has only over the last decade began to influence hospitals and ORs.[21] Greening efforts in the OR should not be relegated to the domain of quality improvement alone; such efforts require meticulous study and ongoing attention to metrics and measurement. Neurosurgeons can establish themselves as thought leaders and team builders in moving these initiatives forward.

Medical waste is often incinerated. The process of incineration releases nitrous oxide and agents known to be carcinogenic including dioxins, furans, and polychlorinated biphenyls into the environment. These toxins have been associated with infertility, hormonal change, diminished fetal weights, and can also increase the acid content in groundwater and soil.[11,22–24] Between 2000 and 2005, Canada enforced strict emissions targets that decreased dioxin and furan emissions by 87%.[25] Thirty-six hospital incinerators in Canada in 2007 produced 85% of the nation's furan and dioxin emissions.[25] Our institution operates a medical waste incinerator, and has made significant investments over the years to improve pollution control systems, as other facilities have likely done so as well. Polluting emissions are highly varied between newer incinerators and older incinerators.

There are a multitude of ways to reduce the OR environmental footprint. Surgical facilities can use unbleached recycled paper instead of chlorine-bleached white paper that releases dioxins into the water supply as a by-product.[26] By using 100% recycled paper, hospitals can reduce manufacturing energy use by 44%, decrease greenhouse gas emissions by 37%, and cut solid waste emissions and water use by 50%.[27] Other ways to reduce waste include decreasing product packaging, using safer cleaning products, and switching to products that are devoid of latex, polyvinyl chloride, and diethylhexylphthalate (used in plasticizers, softeners, adhesives, or solvents).[28] This could reduce allergic reactions, asthma, eye damage, burns, and indirect contamination of hospital food and the water supply.[27] Cleaning chemicals may contribute to the pollution of outdoor air and water supplies, damage to ecosystems, bioaccumulation in animals and plants, and ozone depletion.[29] Patient and staff exposures to cleaning chemicals can cause dermatitis, endocrine and neurologic disorders, musculoskeletal disorders, cancer, asthma, and other respiratory problems.[30-34] Neurosurgeons can become advocates for the health and well-being of the nursing and paramedical staff that support them in their endeavors in the OR by paying attention to these initiatives.

Proper waste segregation in the OR may have the single greatest impact on costs related to waste disposal.[35] Disposal of OR waste requires separation into waste streams, with normal solid waste requiring landfilling and biohazard or regulated medical waste requiring specialized processing. Inappropriate disposal is often due to a lack of awareness among health care workers as to what constitutes biohazard waste.[11,36] Operating rooms can encourage improved waste segregation facilitating access to waste

receptacles and by educating all perioperative staff about what waste requires specialized disposal.[37]

In terms of engaging stakeholders and gaining buy-in for wide-scale recycling efforts, one study found that capital gained from recycling could be used to implement a staff incentive program to improve compliance with recycling. Specifically, providing free coffee or food to staff may help promote recycling behaviors.[14] In our study, we believed that conducting a pilot first within a supportive department with enthusiastic champions would help maximize the possibility of success, gain buy-in, and ensure sustainability among stakeholders prior to an institution-wide roll-out. Although we had a 43% response rate for submission of formal feedback regarding the pilot, we believe that project participants were favorable towards the pilot, as evidenced by daily informal feedback received during the duration of the pilot. We did not interpret the lack of filling out a formal evaluation as a rejection of the program itself. Neurosurgeon leadership of greening and cost efficiency projects is essential to ensure that the voice of the neurosurgeon shapes the initiative and can meet the needs of clinicians in addition to other hospital stakeholders. Neurosurgeons who do not take a leadership role face the risk of having practice changes attempting to mandate efficiency and resource use imposed upon them.

Future areas of exploration might involve comparison of physician or surgeon led efforts for impact and efficacy, as well as whether strict waste reduction initiatives are more or less effective than recycling programs. The size of an institution, and whether a certain OR capacity or case volume is necessary to justify certain types of global recycling efforts is difficult to determine and was a limitation of our pilot, but a question to ask for further studies. Additionally, it would be interesting to assess whether ambulatory surgery centers or other free-standing surgery centers would benefit from such initiatives.

Multiple industries, including manufacturing, industrial engineering, and the energy sector, have been involved in greening and sustainability efforts. In terms of process improvements and iterative learning, these industries could provide medicine and healthcare with valuable lessons as to how greening efforts can be integrated. Change management—or the concept of active managerial control in planning and implementing an institutional change—relies on a mixture of leadership, motivation, culture, project duration, performance integrity, commitment of senior staff, and additional employee effort.[38] Pilot studies, which offer an opportunity to test a proof of concept, allow for employee buy-in and process improvement, before a full roll-out across an institution.

CONCLUSION

Ultimately, surgeons can be effective leaders championing efforts to reduce waste and improve efficiency in the OR. During a 39-d pilot, we collected 1247 pounds of blue wrap (32 lbs daily), saving $31 680.00. Staff response was favorable, demonstrating the feasibility of this type of program. The initiative we outline can be replicated at other centers and not only reduces the environmental footprint, but also may help a department generate additional revenue streams by recycling a necessary packing material that would otherwise require payment for disposal. Such programs should not be relegated to the sphere of quality improvement alone; these initiatives require ongoing, meticulous study and create a significant opportunity for neurosurgeons to improve cost-efficiency and reduce the environmental footprint of the OR.

Disclosures

Funding was received from a Mayo Clinic Values Grant. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: The Emerging Role of Biomarkers in Adaptive Modulation of Clinical Brain Stimulation

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Received, November 30, 2018.
Accepted, February 28, 2019.
Published Online, April 23, 2019.

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From the earliest descriptions of therapeutic neurostimulation in the mid-20th century, it has been recognized that adjustment of stimulator settings based on measured parameters (especially clinical response) is associated with major advantages compared with the permanence of therapeutic lesions. However, these adjustments are generally made intermittently by human programmers; the devices themselves have almost exclusively been "open-loop," providing stimulation that is unchanged between reprogramming sessions. Recent technological developments have made it possible for implanted devices to modify stimulation parameters automatically based on a variety of measurements in order to maximize clinical benefit, and it is now possible to respond in real-time to ongoing physiological changes. Such "closed-loop" approaches have a long and successful history for other medical devices, most notably in treatment of cardiac disease: rate-responsive pacemakers available since the 1980s modify heart rate based on patient parameters such as activity level and cardiac rhythm features, and implanted defibrillators are able to monitor cardiac activity to administer a dose of electrical current in response to dysrhythmia. A similar design for neuromodulation devices (using automatic adjustment to provide stimulation only where or when or how it will have maximal therapeutic effect) seems intuitive, and alteration of stimulator settings in response to measured biological activity should be technologically straightforward. In this context, it is surprising that closed-loop neuromodulation applications are not widespread.

An important next step in creation of these devices will be to use knowledge of physiological abnormalities underlying the expression of neurological disorders in order to identify candidate biomarkers that might be used for automatic device adjustment. In the review article published in this issue of Neurosurgery,[1] the authors summarize philosophies and feedback signals that might be employed in order to continue development of hypothetical closed-loop neuromodulation approaches. They outline recent work to identify biomarkers that could potentially be used for this purpose, including local pathological brain activity, evoked compound action potentials, biochemical changes, electromyography, electrocardiography, and other biological features. In addition to listing different command signal sources, the authors propose a novel five-level classification scheme for different philosophies of closed-loop stimulation based on complexity of signal analysis and discuss disease-specific strategies based on each of them. They conclude that closed-loop technology using these principles could lead to improved efficiency, avoidance of over- or under-stimulation to allow maximize benefits without side effects under changing physiological conditions, and potentially even greater therapeutic efficacy by abolishing pathological activity in real time.

This review is comprehensive and timely, including a description of many recent advances in the field. However, as the authors acknowledge, the practical benefits of fully closed-loop neurostimulation remain largely hypothetical and with a few exceptions the technique has not entered clinical use. Almost all modern adaptive neuromodulation applications involve extracranial stimulation (eg, spinal cord stimulators that adjust stimulation parameters based on patient position and vagal nerve stimulators for epilepsy that are activated in response to changes in heart rate), and with the exception of responsive neurostimulation for epilepsy, all approved intracranial neurostimulators remain "open-loop" between programming sessions. The developments summarized in this article suggest that further progress will require better conception of criteria for developing and validating biomarkers for therapeutic applications as well as rational application of diverse philosophies of responsive stimulation. The advantages of intelligent neurostimulators may still be largely theoretical, but the concepts described in this article will be important for their continued evolution.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: The Emerging Role of Biomarkers in Adaptive Modulation of Clinical Brain Stimulation

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Received, December 10, 2018.
Accepted, March 14, 2019.
Published Online, April 8, 2019.

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While intracranial stimulation is an effective neurosurgical treatment option for certain neurological disorders, traditional implantable neurostimulation devices deliver electrical pulses continuously at preset parameters without adjusting the therapy for the patient's individual symptom(s), medication status, or side effects. Improved patient outcomes and increased implant battery life may be possible through a *biomarker* approach to monitor a patient's disease state, and to adapt the delivery and parameters of stimulation. Such a system is referred to as an *adaptive stimulation* system and is at the center of the review by Hoang and Turner.[1]

In this timely review, the authors recognize the crucial first step in the development of adaptive stimulation therapies as the characterization of biomarkers associated with patient pathophysiology. Intraoperative studies during implantation surgeries, externalizing leads while monitoring patients in neurointensive care facilities facilitate access to brain signals and the study of biomarkers of disease symptoms in acute settings. While intraoperative studies lend themselves to study of network dynamics through the acute placement of intraoperative monitoring electrodes over cortex, external leads overcome issues of ablation effects and limited recording times. Moreover, next generation neurostimulators, such as NeuroPace RNS[2] (NeuroPace Inc, Mountain View, California) and the Medtronic Activa PC + S, Summit RC + S[3,4] devices (Medtronic Inc, Dublin, Ireland) now enable the study of biomarkers of disease symptoms chronically through investigational device exemptions. The authors postulate that for reliable and generalizable operation a biomarker should have the following general characteristics: (i) directly correlated to clinical symptoms, (ii) able to dynamically reflect symptom improvement, (iii) stable in real-world settings and daily activities, (iv) differentiable from background noise, (v) consistent across patients, yet tunable to account for patient variability. The review delves into the most recent intraoperative and chronic studies on biomarkers proposed for the development of adaptive stimulation therapies in light of these characteristics for various disorders, including biomarkers for rigidity and bradykinesia in Parkinson disorder, dyskinesia in Parkinson disorder, freezing of gait in Parkinson disorder, epilepsy, Tourette syndrome, essential tremor, Alzheimer's disease, and depression.

Although the authors' list is comprehensive, it is also important to consider that long-term plasticity is necessary for symptom relief in disorders such as dystonia and depression. It is therefore highly possible that a biomarker capable of reflecting or predicting clinical improvement may be present in a different part of the network than the stimulation target, or may even be different than the biomarker that correlates with clinical improvement. Such a biomarker could guide clinical programming in these disorders, which is very challenging and can take many months, as symptom relief is not immediate. In paroxysmal disorders such as Tourette syndrome or epilepsy, since tics or seizures are not always present, the absence of a tic or seizure biomarker may not be reflective of whether stimulation parameters are optimized. In such cases, a biomarker that directly correlates with observable symptoms may not reflect whether stimulation settings are optimally selected.

Neurostimulator device technology has not progressed significantly from continuous delivery of electrical pulse trains over the last two decades. The authors thus acknowledge the "control mode" as the next system design component for adaptive stimulation. Current and near-future control modes are continuous, scheduled intermittent, responsive, adaptive, and closed-loop stimulation. The control mode is highly dictated by the treatment needs of any particular disease. For instance, rigidity in Parkinson disease would benefit from adaptive stimulation that can be scaled to its present severity, but may suffer from a scheduled

intermittent approach. Or epileptic seizures could be stopped by a responsive stimulation approach, and would not require continuous stimulation. The authors carefully describe each mode in which stimulation therapy is possible.

Overall, the field of neuromodulation is moving towards uncovering biomarkers of disorders and biomarkers of treatment efficacy with the goal of developing smarter implantable neurostimulators for improved symptom relief. Advances in our understanding of disorders through biomarker identification, our understanding of the physiological effects of stimulation, and device technologies that can utilize these biomarkers will better serve patients and clinicians. The design and implementation of these systems will require considerable additional technological advances, as well as many feasibility trials. Neurosurgeons will have a great influence in the development and testing stages of these systems and their clinical translation.

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06/22/2023

Disclosures

Dr Gunduz has funding from NIH R01NS096008, NIH UH3NS095553, NSF 1553482. The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: Predicting Inpatient Length of Stay After Brain Tumor Surgery: Developing Machine Learning Ensembles to Improve Predictive Performance

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Received, July 16, 2018.
Accepted, August 28, 2018.
Published Online, October 17, 2018.

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The authors should be congratulated on their recent manuscript, *Predicting Inpatient Length of Stay After Brain Tumor Surgery: Developing Machine Learning Ensembles to Improve Predictive Performance.*[1] Length of stay (LOS) is an important driver of healthcare cost, particularly in the field of neurosurgery.[2] Using machine learning algorithms, a model was developed that predicted LOS. The authors found that non-white race, non-elective surgery, preoperative weight loss, and sodium abnormalities were the factors most associated with prolonged LOS. These findings are similar to those reported using logistic regression by Dasenbrock et al.[3]

The field of medicine has made many advancements due to "outside the box" thinking. Examples range from the development of germ theory,[4] to the contribution of *Helicobacter pylori* in gastric ulcers formation,[5] to the identification of the link between football and chronic traumatic encephalopathy.[6] Many of these now well regarded concepts represented major departures from the medical dogma of their day. Conception of these innovative ideas required researchers to look at old problems in radically new ways. In the same way, the true potential of machine learning lies not in its confirmation of what researchers are already aware of, but in the introduction of new concepts not yet considered. In 2016, Alphabet Inc., the parent company of Google, introduced AlphaGo (Alphabet Inc., Mountain View, California), a computer program that played the board game Go and defeated some of the world's best human players using AI.[7] The program did so in part by making moves that were alien to human players and would not typically be used in championship level play. Latter iterations of the program have gone on to be even more successful.[8,9] By teaching itself through a novel method of self-learning, AI developed new ways to play a ~2500-yr-old game. Who knows what factors we have been overlooked in the field of medicine and the discipline of surgery?

The above example, along with the referenced article in *Neurosurgery* highlights the potential of machine learning techniques.[1] Yet, despite the promise of machine learning, major issues must be addressed as these tools become ingrained in medicine and the research community. Unlike Go, surgery is not a game. While this is obvious to a clinician, this is not the case for a machine.

First, by itself, what is the value of improved prediction? Genetic testing, which is highly accurate in its prediction, has been available for decades. Yet, its usage in clinical practice remains limited, especially in degenerative disorders such as Huntington's disease, where there are few effective treatments. Understanding risk factors without the ability to modify them, reduces the utility of predictive algorithms. Unfortunately, machine learning does not yet provide insight into modifiability. In the referenced article, non-elective surgeries are associated with increased LOS. But, the electivity of a case is often beyond the control of clinicians. Non-elective surgery is, by definition, associated with rapidly impending clinical deterioration and is generally avoided whenever possible. While this knowledge may help hospitals better predict cost and bed availability, it is not clear how this insight might improve clinical practice.

The more important question is which factors can be modified to improve the outcome, or "end result."[10] Preoperative nutritional status has long been linked with poor outcomes across a variety of surgical fields.[11] It is not surprising that in both machine learning and traditional regression models, pre-operative weight loss is associated with increased LOS.[3] The challenge for clinicians and health services researchers is not just in identifying these risk factors, but in determining how to modify them.[12]

Second, as medicine is not a game with one "best" solution, it will be a challenge

to reconcile AI with human choice—both in terms of physician practice pattern and personal preferences of patients and their families. For instance, there is no universal equation that balances quantity vs quality of life. As any clinician is aware, each patient's opinion on this is deeply personal and can be extremely variable. A computer model may predict the best treatment for a population, but will not know what an individual patient may prefer. When implementing machine learning and AI models, we have to be careful to not minimize the role of individual agency, nor to impose one's own values on patients.

Third, and arguably most importantly, how do we instill ethics into machine learning? Physical restraints are highly effective in preventing falls. While an AI might make such a universal policy recommendation, no clinician would accept it for obvious ethical reasons. While this example might be simplistic, ethical issues can be less obvious, and may reflect larger social problems. For example, minority patients often have worse outcomes. An AI model may be trained to conclude that it is reasonable to expect higher rates of mortality and complications among minority patients. However, an insightful clinician might argue that while race itself is not modifiable, the societal pressures, inequalities, and discrepancies associated with racial disparities are modifiable and worthy of further research and intervention. Over-reliance on machine learning risks codifying these disparities, obscuring the need for minority-specific quality improvement work, and potentially institutionalizing implicit bias. Similar concerns have been raised in the criminal justice system, where computerized models justified harsher sentences on minorities, given the "prediction" that recidivism is higher among minorities.[13] We must take care to not simply camouflage human biases with technology.

Undoubtedly, machine learning represents a powerful tool in the arsenal of the clinical and health services researcher. Through unique insight and novel processing of data, machine learning and advanced AI may come to revolutionize medicine. However, just like any other tool, they must be used responsibly with an understanding of their strengths and limitations.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: Steroid Use Associated With Increased Odds of 30-Day Mortality in Surgical Patients With Metastatic Spinal Tumors in the Setting of Disseminated Disease

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Received, August 7, 2018.
Accepted, September 18, 2018.
Published Online, November 2, 2018.

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The authors[1] utilized the National Surgical Quality Improvement Program (NSQIP) database in order to test for an association between perioperative steroid use and 30-d post-operative mortality among patients undergoing surgery for the treatment of metastatic epidural spinal cord compression (MESCC).[2] In the Supplemental Digital Content portion of the manuscript the authors provide the NSQIP database definition for steroid use:

> "the regular administration of oral or parenteral corticosteroid medications or immunosuppressant medications, for a chronic medical condition, within the 30 days prior to the principal operative procedure. A one-time pulse, limited short course, or a taper of less than 10 days duration would not qualify."

The authors performed a thorough and sound statistical analysis and found an association between preoperative steroid use, as defined in NSQIP, and post-operative mortality (OR 2.48, $P = 0.012$, 7.5% vs 17.6%). The association was independent of medical comorbidity and functional status.

The fundamental limitation of the current study stems from the frequently encountered inability of large national databases to provide adequate detail about treatment and outcome variables relevant to clinical practice. The NSQIP definition of preoperative steroid use fails to capture the majority of dexamethasone-administration practices among physicians who treat MESCC. MESCC requiring surgery generally requires expeditious treatment in order to avoid development or progression of neurologic deficits and/or mechanical instability. Therefore, in modern practice, once MESCC requiring surgery is diagnosed, surgery usually takes place fairly quickly and patients who require surgery for the treatment of MESCC rarely receive steroids for longer than 10 d preoperatively for the treatment of MESCC. Therefore, patients who receive steroids for longer than 10 d represent a small segment of the surgical population or receive chronic steroids for a different indication rather than for the treatment of MESCC. Furthermore, the NSQIP definition specifies that steroids are administered for a chronic condition. This leaves much to interpretation since MESCC generally represents an acute condition, but cancer might be classified as a chronic.

Hobbs et al[1] conducted a systematic review of the evidence for administration of steroids for the treatment of MESCC. Steroid administration for MESCC resulted in neuroprotective effect and improved ambulation in animal and human studies. The authors concluded that based on the overall low quality of evidence, steroid administration is warranted and recommended a rapid taper once therapy is initiated. The lack of surgical studies examining the effect of perioperative steroids represented the crucial limitation of that analysis, since all studies used radiotherapy for the treatment of MESCC. The rapid spinal cord decompression provided by surgery may result in different mechanism and pattern of spinal cord recovery. However, since preservation or improvement of neurologic function serves as the paramount goal of surgical intervention, the potential neuroprotective effect of dexamethasone, albeit with limited evidence, must still be carefully considered when deciding whether it should be administered in patients with MESCC.

In summary, the definition of steroid administration used in the current study precludes any conclusions about the currently recommended practice of dexamethasone administration prior to expeditious treatment of symptomatic MESCC and should not be used as an argument against administration of steroids for preoperative treatment of MESCC. The study shows an association between chronic preoperative administration

of steroids (duration >10 d before surgery) and postoperative 30-d mortality, and this information may be used by the surgeons as one of the mortality risk factors when evaluating the patient for surgery. The authors accurately conclude that the indications and effects of preoperative steroid administration require further study.

Disclosures

Dr Laufer is a Consultant for Globus, Medtronic, DePuy/Synthes, Brainlab, and Spinewave. The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: Radiological Characteristics and Natural History of Adult *IDH*-Wild-Type Astrocytomas With *TERT* Promoter Mutations

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Received, September 9, 2018.
Accepted, October 4, 2018.
Published Online, November 10, 2018.

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Brain tumor diagnosis requires the integration of data from different spheres and investigative modalities. Localization of the lesion remains of foundational importance and is accomplished by clinical acumen and a strong understanding of anatomical–clinical correlation. This is especially important for surgical planning of brain tumor patients. Pioneering tumor neurosurgeons relied upon clinical examination and rudimentary radiological techniques including plain films and air ventriculograms. These provided information on the location of the lesion and occasionally offered additional insight into the nature and biology of the tumor. Bailey and Bucy noted that young brain tumor patients presenting with seizure often had frontal lobe lesions which appeared calcified on plain film.[1] The resected tumor displayed histology reminiscent of oligodendrocytes with regular round nuclei and perinuclear clearing later classified as oligodendroglioma. They also noted favorable prognosis in many such patients. This heralded the start of an era in which clinical, radiological, and pathological information combined to inform on the behavior of brain tumors.

Recently, these metrics have become more clinically impactful with the assimilation of emerging genomic features gleaned from large databases such as the Cancer Genome Atlas.[2-4] Concurrently, It has become clear that molecular features carry significant diagnostic and prognostic importance as they influence the therapeutic responses of brain tumors. In fact, epigenetic profiling of primary tumors has demonstrated superior capability at identifying tumor subtypes than by histology alone.[5] Genomic and epigenomic drivers define brain tumor biology and clinical behavior which may be associated with specific radiological signatures. Conversely, certain radiological features including location, presence or absence of signal circumscription on magnetic resonance imaging, and contrast enhancement may be associated with unique genomic and epigenomic features. The elucidation of such relationships constitutes the rapidly evolving field of radiogenomics or radiomics.[6-8]

The generation of large data sets of genomic and matching radiological data of brain tumors has made radiogenomics a viable, practical, and clinically important endeavor.[9,10] The obvious implication is the ability to predict underlying genomic features and clinical behavior based on routine imaging characteristics performed as part of the initial diagnostic workup in the absence of tumor tissue for pathological assessment. One instructive example is the identification of recurrent mutations in the genes isocitrate dehydrogenase 1 & 2 (*IDH1/2* or collectively referred to as IDH) in infiltrating low-grade glioma (LGG), which leads to the derangement of normal cellular metabolism and results in 2-hydroxyglutarate (2HG) production.[11,12] Subsequent studies have confirmed 2HG as a key player in the pathogenesis of infiltrating LGG.[13,14] Correlation of unique radiological features with the mutational status of *IDH1/2* constituted early examples of radiogenomics in the new molecular era.[15,16] The noninvasive detection of 2HG (as a result of IDH mutation) as a useful clinical tool highlights the rapidity of knowledge translation in this field.[17-19]

Izquierdo et al[20] have contributed to this field with their study of the radiological features of IDH wild-type diffuse astrocytomas with TERT promoter mutations (REF). In a retrospective cohort, they compared the clinical and radiological features of 40 IDH wild-type *TERT* promoter-mutant WHO grade II/III diffuse astrocytomas with 114 IDH-mutant low-grade glioma, 92 IDH wild-type *TERT* promoter-mutant WHO grade IV glioblastomas, and 15 IDH wild-type *TERT* promoter wild-type astrocytomas. They identified association of IDH wild-type *TERT* promoter-mutant WHO II/III diffuse astrocytoma with age of presentation > 50 yr and radiological features of infiltration without contrast enhancement. Also, there is a statistically significant association with

temporal and/or insular localization and interestingly, a growth pattern consistent with gliomatosis cerebri. Also, gyriform infiltration pattern is associated with these particular genomic features. They also noted that most IDH wild-type *TERT* promoter-mutant astrocytomas display rapid growth kinetics while in some cases they may exhibit an initial, falsely reassuring slow growth pattern. These findings add to the burgeoning knowledgebase of genomic, radiological, and clinical features of gliomas. Accumulation of additional data from other cohorts and more in-depth genomic profiling will contribute to additional understanding and further stratification. For example, the inclusion of genomic status of *CDKN2A/B* might further extend the data generated in this study.[21]

The immediate implication of the study by Izquierdo et al[20] is the enrichment of information generated from the routine radiological workup of brain tumor patients and highlight subtle, or under-recognized, radiological features which might have significant diagnostic or treatment importance. This and other similar studies will advance our understanding of glioma formation and progression, undoubtedly providing further insight into its molecular pathogenesis. Finally, integration of deep learning into this workflow will undoubtedly strengthen the connectivity amongst these different diagnostic modalities to increase the precision of diagnosis and inform on prognosis as well as therapeutic options.[22,23]

Disclosures

Dr Yip has received financial compensation for his role as a consultant for Bayer Pharmaceuticals in 2018. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: Radiological Characteristics and Natural History of Adult *IDH*-Wild-Type Astrocytomas With *TERT* Promoter Mutations

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Received, October 8, 2018.
Accepted, November 22, 2018.
Published Online, January 28, 2019.

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The authors of this elegant study[1] retrospectively reviewed the clinical characteristics of 40 gliomas *IDH*-wild-type *pTERT*-mutant astrocytomas (World Health Organization [WHO] grade II [n = 19] and grade III [n = 21]) and compared them to the outcome of 114 *IDH*-mutant and *pTERT*-wild-type lower grade gliomas (LGG), of 92 *IDH*-wild-type *pTERT*-mutant glioblastoma multiforme (GBM), and of 15 *IDH*-wild-type *pTERT*-wild-type astrocytomas. The authors showed that *IDH*-wild-type *pTERT*-mutant astrocytomas typically present as nonenhancing temporo-insular infiltrative lesions or, in some instances, as gliomatosis cerebri in patients aged >50 yr. Accordingly, although these tumors often display an initial, falsely reassuring, LGG-like appearance, they indeed present a typically aggressive behavior and in the absence of treatment, grow rapidly, and develop GBM-like characteristics.

Since their first classification by Bailey and Cushing in 1925,[2] and up to 2007,[3] gliomas have been classified according to their presumed histogenesis, histological aspect, and location. However, since 2007, the discovery that tumors with the same morphology may have different molecular phenotypes,[4] and that molecular phenotype may be prognostically more relevant than morphology,[5] has totally revolutionized the gliomas universe. Thus, molecular features were finally included in the WHO Classification of gliomas in 2016.[6] Accordingly, diffuse astrocytomas were further subclassified on the mutational status of isocitrate dehydrogenase1 and 2 (*IDH1/2*) genes into astrocytomas *IDH* mutant and astrocytomas *IDH* wild type.[6] For the first time in the history of gliomas, a molecular feature was used as a classifier, and this was because it was definitely evident that *IDH*-mutant astrocytomas have significantly better prognosis than *IDH* wild-type ones.[5,7]

However, the real nature of diffuse *IDH*-wild-type astrocytomas still needs to be fully understood. Indeed, this represents a provisional category of astrocytic tumors, which is defined only by the absence of a molecular defect, but that probably gathers biologically and clinically distinct tumors. The majority of diffuse *IDH*-wild-type astrocytomas are GBMs; interestingly, they frequently harbor mutations in the promoter of telomerase reverse transcriptase (p*TERT*) gene, differently from *IDH*-mutant diffuse astrocytomas of all grades.[8]

Major issues relate on low-grade (II and III) diffuse *IDH*-wild-type astrocytomas (LGAs). Should they be considered as glioblastomas? Do they all carry an adverse prognosis? Recent analyses suggest that *IDH*-wild-type diffuse LGAs showing the same molecular profile as *IDH*-wild-type GBM (*pTERT* mutations, epidermal growth factor receptor amplification, chromosome 7 gains or chromosome 10 losses) behave as GBMs.[8] Thus, again, molecular signature seems to be superior than morphological features in the prediction of glioma clinical course.

Histologically, GBM differs from LGAs because it shows microvascular proliferation and/or necrosis.[6] A hypothesis is, therefore, that *IDH*-wild-type LGAs represent early-stage GBMs, which have not yet developed microvascular proliferation or necrosis.[8] Contrast enhancement seen at magnetic resonance imaging (MRI) of GBM probably depends on the presence of microvascular proliferation, which increases blood-brain barrier permeability.[9] This accounts for the possible presence of nonenhancing GBMs.[9] Indeed, GBMs having necrosis, but not microvascular proliferation, do not show contrast enhancement at MRI.[9] In addition, although *IDH*-wild-type diffuse LGAs with p*TERT* mutations are presumably early-stage GBMs and will progress to "fully-defined" GBMs, they do not show contrast enhancement, similarly to *IDH*-mutant diffuse LGAs.

Thus, as contrast enhancement is not helpful in the identification in such "early-stage" GBMs, how could they be preoperatively identified? Since radical surgical resection is a major

prognostic factor in *IDH*-wild-type diffuse LGAs, the identification of radiological features able to differentiate those tumors from *IDH*-mutant LGAs would be extremely important for subsequent surgical procedure. In this sense, this study provides a significant contribution to our understanding of behavior and radiological appearance of such tumors, which may result in better clinical management of patients.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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06/22/2023

Commentary: Evaluating the Landscape of Clinical Research in Neurosurgery

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Received, January 22, 2019.
Accepted, January 23, 2019.
Published Online, May 23, 2019.

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The traditional clinical research journey begins with a question, proceeds through design and conduct of the study, and culminates in publication in a scientific journal. In the paper 'Evaluating the Landscape of Clinical Research in Neurosurgery',[1] the authors attempt to quantify how many neurosurgical research studies make it to final publication. The abridged version: 'not many', with a mere 22% of registered studies resulting in publication in an indexed journal.

While the limited publication rates described in the paper is concerning, it is perhaps not surprising. Studies in the analogous fields of stroke,[2] dementia,[3] and neurology[4] have described similar rates of nonpublication. In a systematic review of surgical trials, publication rates were equally lamentable, with one fifth of trials never completing and 1 in 3 of the remainder never published.[5]

While the neurosurgical publication rate described in this paper is undeniably low, the true scale of nonpublication may be even greater. In their paper, the authors used the ClinicalTrials.gov registry as substrate, utilizing electronic searching to identify registered neurosurgical research projects. This approach, whilst valid, is not the only germane method. In other studies, authors have described rates of publication of research approved by ethics committees,[6] presented at a conference,[3] or identified in bespoke research repositories such as those curated by Cochrane review groups.[7]

The limitation of basing the denominator on studies held within the Clinical Trials resource, is that it assumes all research is registered with Clinical Trials in the first place. Historically, fewer than half of surgical trials were adequately registered[8] and so it seems likely that many studies were missed. By limiting to a single, predominantly North American, database a substantial proportion of the international neurosurgical literature would also be missed. We can speculate as to whether similar nonpublication would be seen if the same searches were conducted within the World Health Organization International Clinical Trials Registry Platform or the EU Clinical Trials Register. Differences in regulatory practices, funding arrangements, and the milieu of clinical neurosurgery could all create international divergence in publication practice.

The authors adopted an inclusive approach and considered any form of neurosurgical research in their analysis. Again, Clinical Trials may not be the optimum arena for this. While registration of trials is mandated by many funders and journals, including Neurosurgery, the registration of other research studies such as observational epidemiology and diagnostics is less common.[9] Searching an electronic database for a broad concept such as 'neurosurgical research' is also problematic. The authors used single terms to identify research on common neurosurgical conditions. The potential for underestimation is once more apparent since single term searching will not identify all relevant research. In the Cochrane dementia group we developed syntax of over 20 different synonyms for dementia to counter this issue.[10]

Thus, rates of nonpublication of neurosurgical research are at least as poor, if not worse, than those reported in the paper. There are many reasons why we should be alarmed by this. Publication should not be the sole reserve of the definitive, positive intervention trial. Even studies, which do not demonstrate significant results, have value in advancing our knowledge and informing future research. At best, nonpublication of research can result in needless duplication and waste of financial resources. At worst, it can bias our understanding and skew guidelines and practice. This becomes particularly pressing when collating research in systematic review and meta-analysis. These are not merely theoretical concerns, there are many high profile examples where nonpublication of research data has led to erroneous treatment recommendations. Thankfully the landscape is changing and international collectives are working to ensure all trials are in the public domain.[11]

Clearly, communication of research is important to clinicians, researchers, policy makers, and ultimately patients. Aside from the

scientific arguments, there is an explicit ethical imperative. Clinical research is contingent upon individuals who have consented to assist in the credible anticipation that this will improve future patient care in an altruistic endeavor. By failing to share research findings, we are doing these volunteers a disservice.

Lastly, let us consider the matter of visibility of research. The authors outcome of choice was publication in a PubMed listed scientific journal. Although no researcher would claim that achieving scientific publication is easy, with the exponential increase in biomedical journals the options for achieving some form of publication are increased. With this increasing volume of research, does publication still guarantee visibility to the potential end users of the research and can publication within a journal be considered synonymous with research impact? Funders and research centers are reconsidering how we define and measure the clinical footprint of research. Increasing attention is being given to describe which platforms are garnering the most attention/dissemination in this age of social media, internet usage and data sharing. What seems clear is that traditional measures of impact such as journal impact factor have only a limited association with alternative metrics such as social media mentions.[12] There is also the suggestion that neither traditional nor altmetrics are a good yardstick of the methodological quality of the study or its reporting.[13]

So, what can we conclude from this paper? Nonpublication is an issue for neurosurgical research and there is reason to believe that nonpublication is the norm. This nonpublication has ethical, scientific, and policy related consequences. However, even when a research project is published there is no guarantee of visibility and impact. We must find ways to facilitate timely publication and exploit the many new opportunities for sharing results beyond the traditional print journal.

Disclosures

Dr Quinn is supported by a joint Chief Scientist Office and Stroke Association Fellowship. Dr Quinn is editor coordinating of the Cochrane Dementia Group and member of the UK NIHR Complex Review Support Unit. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: Greening the Operating Room: Results of a Scalable Initiative to Reduce Waste and Recover Supply Costs

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Received, May 8, 2018.
Accepted, June 1, 2018.
Published Online, July 27, 2018.

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As for the future, your task is not to foresee it, but to enable it.

—Antoine de Sainte-Exupery, "The Little Prince"

Practicing neurosurgery is ever more complex. Regulations abound, revenues are dropping while expenses rise, and public scrutiny and expectations are enormous. Given these tremendous challenges, why should neurosurgeons care about environmental issues? As a specialty, neurosurgery has long championed the pioneering spirit, rewarded individual drive, and been a driving force for all of medicine. Unfortunately, we have also demonstrated a tendency at times to become fractured within our small community, insular, and resistant to change. At this moment, all neurosurgeons must embrace ingenuity, diversity, and progress to sustain the future of neurosurgery and thus continue to relieve the suffering of our patients. This includes caring for our environment. Consider that health care is:

- A leading consumer of energy, water, and other valuable resources
- It accounts for 25% of fossil fuel usage in the US
- The second leading producer of waste, more than 33 pounds per hospital bed every day, and
- Medical waste is at least 119% higher cost than regular waste ($.50 per pound vs $.03).

However, this also means there is the potential for meaningful transformation that benefits patients, health care providers, the environment, and the bottom line.

There are at least 3 compelling reasons for neurosurgeons, such as the authors of "Greening the Operating Room: Results of a Scalable Initiative to Reduce Waste and Recover Supply Costs"[1] to be pioneers in these efforts. First, neurosurgeons are disproportionately represented in the leadership of our hospitals and communities. Without our support, moving such endeavors forward will be challenging. Second, increasing studies of the clinical impact of such changes (a burgeoning field known as evidence based design) demonstrate benefits such as how natural light decreases complication rates, reduce narcotic use, and diminish length of stay. In most hospitals, nurses spend 29% of their time walking, time they are not spending on patient care. Careful workplace design can dramatically improve workflow and thus improve overall quality and patient safety. The final reason is because if we ask the question, "What would we want if the patient were our spouse, our parent, or our best friends?" the answer would be a warm, comfortable, single room with an abundance of natural light, comfort for our caregivers, health care personnel not overtaxed by unnecessary distances to walk, and meals that promote healing and well-being.

In the United Kingdom, the National Health Service has established a major initiative to insure the "Expectation that sustainability (in health care) will become the norm" and that eventually, "sustainability will become routine, culturally embedded and self-regulatory." The US lags behind in these endeavors. This manuscript offers wonderful insights into how every neurosurgeon can initiate a process that explores opportunities small and large that can have a positive impact on the environment. There efforts should be applauded and many more should follow their example.

Do not go where the path may lead; go instead where there is no path and leave a trail.

Ralph Waldo Emerson

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Commentary: The Florida Youth Concussion Law: A Survey-Based Observational Study of Physician Practices and Their Legislative Awareness

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This article was previously presented as: (1) Stelzer JW, Sbeih FK, Field M. A descriptive analysis of adherence to established guidelines by Florida physicians managing concussions in youth athletes. Poster at 2016 Congress of Neurological Surgeons Annual Meeting, San Diego, California, September 24-28, 2016; and (2) Stelzer JW, Sbeih FK, Field M. A descriptive analysis of the diagnostic and treatment modalities utilized by Florida physicians managing concussions in youth athletes. Poster at 2016 American Academy of Neurology Sports Concussion Conference, Chicago, Illinois, July 8, 2016.

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Received, April 14, 2018.
Accepted, March 18, 2019.
Published Online, June 19, 2019.

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Approximately 38 million American youths participate in organized sports each year.[1] Although reported concussions were estimated around 395 000 in high school athletes during the 2008-09 academic year,[2] yearly concussion rates have been shown to increase as high as 15.5% each year over a recent decade.[3] Moreover, concussions account for 8.9% to 13.2% of all reported injuries in high school athletics, making the need for concussion awareness paramount.[4-8]

A concussed brain appears normal with traditional neuroimaging like computed tomography and magnetic resonance imaging, but symptoms affecting consciousness, cognition, emotional lability, and sleep can remain from days to months.[9-16] Second impact syndrome (SIS) is a poorly understood clinical entity that may occur if an additional head impact is sustained while symptoms of a prior concussion remain.[17] SIS can lead to prolonged and more severe symptomology or increasingly critical outcomes such as malignant cerebral edema, permanent disability, or death.[18-20] Although SIS is rare, it may be very possible if return to play (RTP) to sport is premature. The majority of SIS victims have been adolescents, not surprisingly, because adolescent athletes also have a much slower return to pre-concussive baseline compared to adult athletes.[21-23] To complicate the issue, youth athletes may not be inclined to report concussive symptoms or follow RTP protocol after concussion.[24] This data has prompted coaching and medical staffs to closely monitor concussed youth athletes, but adherence to the established RTP guidelines have not been studied.

Currently, the accepted RTP protocols for concussed athletes are outlined by the Consensus Statement on Concussion in Sport, 5th international conference,[10] the American Academy of Pediatrics (AAP),[25] and the American Academy of Neurology (AAN).[26] These protocols have highlighted the need for comprehensive neuropsychological (NP) testing in combination with physician-performed medical assessments. The recommendations also require a step-by-step evaluation during a gradual return to sport, spanning at least 6 d.[10] In 2012, the state of Florida passed legislation requiring clearance for RTP by state licensed allopathic or osteopathic physicians.[27] The Florida statue reads: "Medical clearance must be authorized by the appropriate health care practitioner trained in the diagnosis, evaluation, and management of concussions as defined by the Sports Medicine Advisory Committee of the Florida High School Athletic Association." The Florida statue differs from other state legislation requiring only a healthcare 'practitioner' to clear athletes for return to play. Although the law has eliminated nonmedical professionals from the decision for RTP, 2 problems still arise.

First, the majority of physicians clearing athletes for RTP are pediatricians and family medicine physicians, who may not have the resources or training necessary to accurately manage concussions.[28] Second, neuropsychologists, who give clinicians integral insight into concussion management due to their unique ability to interpret cognitive assessments, are legally excluded from the RTP decision making process simply because they are not physicians.[29] The dearth of NP testing for youth athletes stems from a myriad of factors including physician preference and accessibility. However, it is important to note that in the absence of individual NP testing data, published normative data for age and gender can be used as surrogate.[30-32] Regardless of cause, NP is not currently utilized effectively, with certain studies reporting up to 75% of concussed high school football players lacking NP testing to guide RTP.[33] Athletes may appear physically ready for RTP, but NP testing may demonstrate that the brain is still in a state of healing. Athletes that

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do not undergo recommended NP testing are more likely to RTP much sooner than athletes that do undergo NP testing.[33] This premature athletic return could have severe negative consequences.

A knowledge gap still exists in the areas of Florida physicians' legislative awareness and concussion management. Specifically, no studies have looked at the Florida concussion legislation's impact on youth concussion management. This study was aimed at describing the legislative awareness and concussion management in youth athletes of physicians practicing in the state of Florida.

METHODS

Procedure and Design

This was an observational online survey study of Florida physicians. Surveys were sent via email; the web-based survey software Qualtrics was used for distribution (Provo, Utah). Follow up emails were sent to non- and partial-respondents 2 and 4 wk after the initial request. The survey was closed 6 wk after the initial request. The IRB at the University of Central Florida reviewed and determined this study Exempt Human Research (SBE-15-11347).

Participants

Physicians board-certified by the Florida Board of Medicine practicing in family medicine, pediatrics, emergency medicine, neurology, and orthopedics were included. These specialties were chosen due to their primary or secondary care nature in concussion diagnosis, management, and return to play practice. Neurosurgeons were excluded due to its tertiary care qualities. Email addresses were obtained from the Florida Board of Medicine's public registry.

Instrument

A 21-question, researcher-developed survey was used (**Appendix, Supplemental Digital Content**). The survey included 19 multiple-choice questions, including 5 clinical vignettes (not analyzed) and 2 free-text questions that gathered information regarding patient concussion management and clearance for athletic return in the "last 2 years" (Q5 and Q8). To assess face validity, a preliminary survey was reviewed by independent researchers and physicians. Some syntax edits were made based on the recommendations given to the researchers and 1 question was added (Q9).

Data Management and Statistical Analyses

A total of 657 responses were collected (8.5% response rate); of those responses 102 (15%) did not respond to more than 3 questions and were removed from the dataset. The remaining responses (n = 555) were as follows: 531 (96%) complete responses and 24 (4%) partial responses. Of the complete responses, 162 (29%) were from physicians that did not diagnose and manage youth concussions. Thus, samples size is 393. For thoroughness, the overall data is reported in the 'diagnosis/management and clearance of athletes' section of the results. However, the remaining analyses include only physicians that diagnose/manage and clear youth (n = 254).

Categorical variables are reported as n (%; Qs 1-4, 6, 8-21). Question 3 was coded into additional categories that arose from the "other" response option. Three questions (Q10, Q11, and Q12) were dichotomized as "correct" and "incorrect." Continuous variables were expressed as mean ± standard deviation and median (IQR; Q5 and Q7). Furthermore, number of athletes diagnosed/managed and number of athletes cleared were dichotomized as (≤30 and ≥30). Two simultaneous logistic regressions were performed to determine which medical specialty was more likely to diagnose/manage and clear. Odds ratio (OR) and 95% confidence intervals (CI) are reported. Statistical analyses were conducted using SPSS 25.0 (IBM; Armonk, New York).

RESULTS

Overall Diagnosis/Management and Clearance of Athletes

Most physicians (374; 95%) reported that in the last 2 yr (2014-2016), they did not receive any sport concussion training from the Florida Board of Medicine. However, 369 (67%) physicians had diagnosed/managed a youth athlete with a sport-related concussion in the same period. The 3 medical specialties highly represented were: emergency medicine (133; 36%), pediatrics (85; 23%), and family medicine (81; 22%).

The overall number of concussed youth athletes that physicians diagnosed/managed in the last 2 yr was 25 ± 52. Moreover, of the physicians who diagnosed/managed, 84% (310) reported that they diagnosed/managed at least 30 concussed youth athletes in the last 2 yr (Table 1). In the same period, 44% (254) of physicians surveyed cleared a concussed youth athlete to RTP. Overall, physicians cleared 16 ± 41 youth athletes. Physicians that cleared were more likely to be in family medicine (81; 33%) and pediatrics (68; 28%; Table 2). Whereas, 56% of physicians that diagnosed/managed also cleared, still some reported that they never cleared to RTP, 139 (34%, only diagnosed/managed).

Considerations in Diagnosis/Management and Clearance

A total of 254 physicians diagnosed/managed *and* cleared athletes (Table 3). To guide concussion management, physicians used several resources; 51% (129) used grading scales for assessment and 87% (221) reported use of one or more published guidelines. Most reported use of some clinical testing: neurological testing (66%), neuropsychological testing (48%), and/or functional testing (6%). A majority used physical symptoms (237; 93%) and neuroimaging 95 (37%; Table 4). The recommended RTP guideline, 'Light aerobic exercise without resistance training and monitor for symptoms,' was followed by 47% (118) of physicians. Physicians (220; 87%) that cleared a high volume of patients (≥30 concussed in the last 2 yr) used similar criteria to guide clinical management (Table 4).

When assessing the number of modalities used, most physicians (200; 79%) relied on multiple modalities: 35% (70) used 2 modalities, 39% (77) used 3 modalities, and 26% (53) used 4 or 5 modalities. When physicians used only 1 modality (51; 20%), they most often relied on physical symptoms (40; 78%), followed by neuropsychological testing (7; 14%), neurological testing

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TABLE 1. Sports Related Concussions That Were Diagnosed and Managed by Specialty (n = 369)

Medical specialties	Diagnosing/managing physicians (n = 369)	Mean ± SD	Median (IQR)	Diagnosed/managed ≥30 patients (n = 310)
Emergency medicine	133 (36)	33 ± 59	15 (6-30)	102 (33)
Family medicine	81 (22)	19 ± 38	5 (2-75)	70 (23)
Neurology	30 (8)	40 ± 102	10 (4-24)	25 (8)
Orthopedics	18 (5)	5 ± 13	5 (2-16)	17 (6)
Pediatrics	85 (23)	15 ± 18	10 (4-20)	78 (25)
Other[a]	22 (6)	27 ± 45	8 (4-23)	18 (6)

Data reported as n (%), mean and standard deviation (SD), and median and interquartile range (IQR).
[a]All other physicians not in the included specialties.

TABLE 2. Sports Related Concussions That Were Cleared by Specialty (n = 254)

Medical specialties	Physicians that cleared (n = 254)	Mean ± SD	Median (IQR)	Cleared ≥30 patients
Emergency medicine	38 (15)	16 ± 40	6 (2-15)	35 (15)
Family medicine	82 (32)	17 ± 35	5 (2-10)	73 (31)
Neurology	30 (12)	26 ± 81	7 (4-11)	26 (11)
Orthopedics	17 (7)	8 ± 8	4 (2-13)	15 (6)
Pediatrics	70 (28)	14 ± 25	7 (3-17)	68 (29)
Other[a]	17 (7)	6 ± 36	6 (2-10)	17 (7)

Data reported as n (%), mean and standard deviation (SD), and median and interquartile range (IQR).
[a]All other physicians not in the included specialties.

TABLE 3. Sports Related Concussions for Physicians That Diagnosed, Managed, and Cleared by Specialty (n = 254)

		# of youth diagnosed and managed			# of youth cleared		
Medical specialties	# Physicians	Mean ± SD	Median(IQR)	≥30 Patients	Mean ± SD	Median (IQR)	≥30 Patients
Emergency medicine	38 (15)	41 ± 85	20 (9-36)	28 (74)	16 ± 41	6 (2-15)	35 (92)
Family medicine	82 (32)	18 ± 37	5 (2-10)	72 (88)	17 ± 35	5 (2-10)	73 (89)
Neurology	30 (12)	40 ± 102	10 (4-25)	25 (83)	26 ± 81	7 (4-11)	26 (87)
Orthopedics	17 (7)	11 ± 13	5 (2-18)	16 (94)	8 ± 4	4 (2-13)	17 (100)
Pediatrics	70 (28)	17 ± 27	10 (5-20)	65 (93)	14 ± 25	7 (3-17)	68 (97)
Other[a]	17 (7)	25 ± 40	10 (4-25)	14 (82)	17 ± 36	6 (3-10)	15 (88)

Data reported as n (%), Mean and standard deviation (SD), and Median and Interquartile range (IQR).
[a]All other physicians not in the included specialties.

(2; 4%), and neuroimaging (2; 4%). Interestingly, 1% (3) of physicians did not report the use of any modalities.

Athlete Assessment and Referral

Most physicians thought that a team physician (76; 30%) is most qualified to assess an athlete for a sport related concussion, followed by a neurologist (61; 21%), and an athlete's primary care physician/pediatrician (55; 22%). Almost half, 49% (123) reported they refer out; the most common referral was to a neurologist (21%). Assessment and referral by medical specialty are reported in Table 5.

Training, the Law, and Recommendations for Safety Laws

A total of 71% (179) of physicians had adequate training to prescribe a RTP protocol, and (35%; 89) were aware of a youth concussion law in the state of Florida. A total of 42% (107) believe a youth concussion law should state that RTP clearance for sport

TABLE 4. Diagnosis and Management Modalities of Physicians

Diagnosis/management modalities used	Managed/diagnosed and cleared (n = 254)	Physicians with ≥30 Patients (n = 220)
No guidelines	33 (13)	30 (14)
Grading scale	129 (51)	114 (52)
Physical symptoms	237 (93)	204 (93)
Neurological testing	168 (66)	141 (64)
Neuropsychology	121 (48)	102 (46)
Neuroimaging	95 (37)	81 (37)
Functional testing	16 (6)	10 (5)

Note: All values given in N (%).

TABLE 5. Physician Athlete Referral by Medical Specialty

	Emergency medicine	Family medicine	Neurology	Orthopedics	Pediatrics	Other
No referral	6 (16)	55 (67)	18 (60)	3 (18)	38 (54)	11 (65)
Athlete's PCP/pediatrician						
Qualified	---	23 (28)	3 (10)	---	28 (40)	1 (6)
Referred	14 (37)	4 (5)	---	1 (6)	4 (6)	---
Athletic trainer						
Qualified	2 (5)	6 (7)	---	---	4 (6)	---
Referred	1 (3)	2 (2)	---	---	---	---
Chiropractor						
Qualified	---	1 (1.2)	---	---	7 (10)	---
Referred	---	---	---	---	---	---
Emergency medicine physician						
Qualified	13 (34)	5 (6)	---	---	11 (16)	2 (12)
Referred	1 (3)	1 (1)	---	---	1 (1)	1 (6)
Neurologist						
Qualified	9 (24)	7 (9)	24 (80)	7 (41)	5 (7)	3 (17)
Referred	11 (29)	13 (16)	2 (7)	9 (53)	16 (23)	3 (18)
Neuropsychologist						
Qualified	4 (11)	2 (2)	1 (3)	3 (16)	2 (3)	2 (12)
Referred	---	2 (2)	6 (20)	---	4 (6)	3 (12)
Neurosurgeon						
Qualified	---	---	---	1 (6)	---	1 (6)
Referred	---	---	---	1 (6)	1 (1)	---
Orthopedic surgeon						
Qualified	---	---	---	1 (6)	---	---
Referred	---	2 (2)	---	---	---	---
Team physician						
Qualified	10 (26)	38 (46)	2 (7)	5 (29)	13 (19)	8 (47)
Referred	---	---	---	---	---	---
Sport Medicine						
Qualified	---	---	---	---	---	---
Referred	1 (3)	2 (2)	1 (3)	3 (18)	4 (6)	---
Concussion Clinic						
Qualified	---	---	---	---	---	---
Referral	2 (5)	---	---	---	1 (1)	---
Other						
Qualified	---	---	---	---	---	---
Referral	1 (3)	---	1 (3)	---	1 (1)	---

Data are reported as n (%).
- - -: No data to report in this category.

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should come from a licensed allopathic or osteopathic physician, and (147; 58%) believe a youth concussion law should state that at least one of the following should also be assessed or utilized for RTP clearance to sport: neurological testing (2; 8%), neurocognitive testing (33; 13%), exertional testing, (12; 5%), or clearance from a healthcare provider with specialized concussion training (81; 32%).

Medical Specialties as Predictors of Diagnosis/Management and Clearing

Family medicine physicians were more likely than any other specialty to *diagnose and manage*, this was only significantly different from orthopedic physicians ($P < .001$). The odds of *diagnosing and managing* a concussed youth decreased for emergency medicine [OR: .58 (CI: .286-1.179)] and orthopedic [OR: .16 (CI: .072-.366)] physicians. However, the odds of *diagnosing and managing* a concussed youth increased for pediatricians [OR:1.014 (CI: .518-1.987)] and neurologists [OR:1.722 (CI: .728-4.075)].

As compared to family medicine physicians, the odds of *clearing* a concussed youth increased for all other specialties: emergency medicine [OR: 9.429 (CI: 1.215-73.178)], orthopedics [OR: 78.947 (CI: 10.399-.599.353)], pediatricians [OR: 12.927 (CI: .351-24.396)], and neurologists [OR: 3.529 (CI: .298-41.856)]. Although family medicine physicians were less likely than any other specialty to *clear* concussed youth, this was significantly different for orthopedic ($P < .001$) and emergency medicine physicians ($P = .032$). Family medicine physicians were more likely to diagnose and manage, but less likely to clear and orthopedic physicians were less likely to *diagnose/manage* and *clear.*

DISCUSSION

Understanding of the dangers of sports-related concussion has significantly improved over the past decade. In 2009, the first legislation related to sports-related concussion, the Lynstedt Law, was passed in Washington State to mitigate this danger. Since, all states in the US have passed legislation. In broad strokes, these laws tend to follow the same pattern.[34,35] They include (1) some form of education to players, coaches, trainers, etc; (2) immediate athlete removal from play when a concussion is suspected; and (3) medical clearance before RTP.[27,35,36] These measures have helped address youth athlete concussion in the US, but there may be several issues that remain to be addressed. To date, few studies have examined the impact of these laws and there is insufficient research to explore the implementation and effectiveness of these legislations.[34,37-39]

The present data suggests that many of the physicians treating concussed youth athletes in the state of Florida are not adequately trained to diagnose and manage concussions in the context of safely clearing the youth athlete for RTP to sport. This is evidenced by the 220 most experienced respondent physicians that diagnosed/managed and cleared at least 30 concussed youth athletes in the last 2 yr are only utilizing literature-recommended neuropsychological testing about 40% of the time. It is important to note that the dearth of NP testing for youth athletes stems from a myriad of factors including the condition's chronicity, physician preference, and accessibility. Furthermore, in the absence of individual baseline NP data, published normative data for age and gender can be used as surrogate. Regardless of cause, data suggests that NP testing is not utilized as often or as effectively as it may be. Additionally, physicians default to neuroimaging and concussion grading scales even though these methods have been proven to be ineffective in the diagnosis and management of concussions. The data show that up to a quarter of the physicians diagnosing, managing, and ultimately returning concussed athletes back to athletic competition are not adhering to any published guidelines or criteria to direct their clinical judgment.

To further discuss the problems with clearance for RTP, we can look at the emergency medicine physician group as an example. The data suggest that approximately 14% of the physicians clearing youth athletes for RTP are emergency physicians. This is concerning since the nature of the emergency medicine (EM) practice would yield itself to likely evaluate the concussion initially, but not follow the concussed youth athlete for repeat evaluations. When RTP decisions are made at the time of injury, the aforementioned problems such as a lowered threshold for subsequent concussion risk put the patient at risk. Although EM physicians are an integral part of concussion diagnosis and initial management, the RTP decisions are likely best made by physicians who have the ability to perform serial evaluations during the established RTP protocol guidelines.

The state of Florida passed a law to protect youth athletes from returning to athletic competition without physician clearance. However, our study shows that only about 35% of physicians that are diagnosing, managing, or clearing are even aware that such a law exists. Some may suggest that this unawareness is because the law only applies to physicians actively managing concussions and clearing youth athletes for sport, but unfortunately the law does not apply only to physicians with specialized concussion training or experience. Moreover, the data shows that the percentage of physicians aware of the legislation decreases from 35% to 33% within the group of physicians who clear a significant number of concussed athletes for RTP (≥30 patients). If even physicians who regularly clear youth athletes to RTP are generally unaware of the state legislation, it is reasonable to surmise that they are not adhering to it.

Over 48% of Florida physicians do not feel adequately trained even when they may be using valid tools and techniques. Over 80% of those surveyed reported that they would like further concussion training and over 95% reported no concussion-specific training since the youth concussion law was passed in 2012. These factors may result in concussed youth athletes receiving suboptimal health care with the possibility of a premature RTP to sport and create the potential for detrimental effects if the youth sustains a subsequent concussive injury.

Solutions to the problems outlined could potentially come from many avenues, and may well require amendments to

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legislation, including the identification of specific health care providers that are better suited to manage and clear concussed youth athletes or specify training for those who do. Logistically, this might be a difficult task for physicians and patients alike, especially if Florida were to restrict the duty to limited medical specialties in an attempt to ensure baseline training. It may also be of benefit to legally include neuropsychologists in the clearance of youth athletes, given certain requirements of training. We recognize that improved legislation alone may not resolve the current issues surrounding state mandates concerning management of sport-related concussion. For example, lack of awareness by physicians of such laws may be a potential issue. Outside of specific legislative changes, awareness is an important facet of change, and our study demonstrates awareness of current legislation is lacking. Although recently dedicated conferences and meetings surrounding the topic of sport-related concussions have begun, a continued interest in those conferences for both health professionals and nonhealth professionals alike may be of benefit. Including youth concussion conferences or awareness bulletins for those outside of the healthcare profession (eg, parents, coaches) could empower caregivers and patients, giving them much needed information concerning concussions and the RTP process. The onus is not simply on the physicians to guide RTP, but the patients as well since they will be able to make more informed decisions regarding their care. For those involved in healthcare, a feasible campaign may be to implement programs to more effectively increase awareness and concussion education to the physicians already included in legislature. The challenge of increasing physician awareness and adherence to clinical guidelines has been well established, since physician culture, beliefs, and habits have been discussed as notable barriers to change.[40] Integrating concussion training into licensure renewal, offering concussion-specific CME credits, and organizing county- or state-wide concussion conferences could enhance awareness and compliance. Additionally, encouraging innovation and improvement of information technology systems and electronic medical records may improve physician adherence. For example, if hard stop alerts were implemented prior to the discharge of pediatric patients with a diagnosis of "concussion," a physician would have to consciously answer questions regarding return to activity. In summary, the physician awareness of and adherence to clinical guidelines is multifactorial; therefore, a multifaceted approach to improvement is necessary for change.

This study provides insight into the real problems that exist between legislative mandates and practical application in patient clinical care. Potential issues related to our study include some inherent bias or lack of clarity within survey question items and answers that may have unknowingly occurred. The authors attempted to prevent this by assessing face validity through independent review.

Selection bias is always a challenge in self-selecting participation. For example, participant physicians might feel more comfortable with the subject matter or might have had an increased interest in the content of the investigation. It is also possible that physicians who did not clear youth athletes to RTP may not have responded because they felt the study did not apply to them. This study attempted to reduce researcher-based selection bias by sending surveys to every Florida Board of Medicine board-certified physician (n = 7716) practicing in specific specialties rather than trying to target those who commonly treat concussed youth athletes. Nonetheless, this decision had a direct impact on response rate. In our study, response rate is lower than other published literature on physicians, but similar in number of responses.[37] Traditionally, physician surveys generate lower than average response rates due to time constraints and low survey prioritization relative to career duties.[38,39]

Future research analyzing the practices of concussion diagnosis, management, and RTP are needed to further describe the potential shortcomings in clinical practice. An expanded study may include geographic regions or sport-specific RTP research would be beneficial to identify the scope of discrepancies between legislation and clinical practice on a broader scale. Finally, although many of the state youth concussion laws are similar, an analysis among legislation variations and their clinical effectiveness may give insight into the factors that could optimize clinical care.

CONCLUSION

To our knowledge, this is the first study analyzing physician concussion management practices post statewide legislation related to RTP clearance in the concussed youth athlete in the state of Florida. Two conclusions can be made. First, there is a lack of awareness and adherence to the Florida youth concussion law. Second, many of the physicians that are following the law are doing so in a nonevidenced based manner. Although the legislation was well-intentioned, the incomplete protection provided by this legislation potentially places vulnerable youths at risk of having significant long-term disability or even death related to RTP clearance prior to full recovery. In sum, this study sheds some light on opportunities to improve concussion care.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental Digital Content. Appendix. Researcher-Developed Youth Concussion Survey for Determination of Youth Concussion Diagnosis, Management, Return-to-Play Protocol, and Legislative Awareness. This survey gives an example of the questions answered by the respondent physicians.

COMMENT

This important commentary article highlights the return to play (RTP) decision-making variability seen in a sample of Florida physicians managing concussion in athletes. Florida is relatively unique in that a state law passed in 2012 requires concussed athletes to be cleared by a physician, whereas most other states allow an athlete to be cleared by a healthcare 'practitioner' including a neuropsychologist. As the authors astutely point out, the Consensus Statement on Concussion in Sport, 5th international conference, the American Academy of Pediatrics (AAP), and the American Academy of Neurology (AAN) recommend neuropsychological testing as part of a comprehensive RTP protocol. Despite this, many physicians do not utilize neuropsychological testing when weighing their RTP decision. Consistent with prior research, this survey found that less than half of sampled physicians included neuropsychological testing in their management modalities, and in general there was inconsistency in the number of modalities used when managing concussions. The variability in areas such as awareness of the law, infrequent use of exertional testing, and reliance on neuroimaging to guide RTP underscores the importance of a multimethod and multidisciplinary approach to management of sport-related concussion.

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Interstitial Stereotactic Laser Anterior Corpus Callosotomy: A Report of 2 Cases with Operative Technique and Effectiveness

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Received, December 13, 2017.
Accepted, May 25, 2018.
Published Online, July 5, 2018.

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BACKGROUND AND IMPORTANCE: Corpus callosotomy is an effective palliative treatment for medically intractable Lennox–Gastaut syndrome (LGS) that disrupts the interhemispheric synchronization of epileptiform discharges. However, traditional open corpus callosotomy carries a significant risk of surgical complications associated with craniotomy and a parafalcine approach to the corpus callosum. Here, we report 2 cases of anterior corpus callosotomy using MRI-guided stereotactic laser interstitial thermal therapy (LITT) as a minimally invasive technique for mitigating the risks of craniotomy while achieving favorable outcomes.

CLINICAL PRESENTATION: Two patients with medically intractable LGS underwent stereotactic laser anterior corpus callosotomy using a 2 laser-fiber approach. Ablation of 70%-80% of the corpus callosum was confirmed by postoperative MRI diffusion tensor imaging and volumetric analysis. Marked reduction of epileptiform activity was observed in both patients during postoperative video-EEG studies as compared to preoperative video-EEG studies. Freedom from disabling seizures including drop attacks was achieved in 1 patient for 18 mo, and more than a 90% reduction of disabling seizures was achieved in the other patient for 7 mo with cognitive improvement and without surgical complications.

CONCLUSION: These early data demonstrate the technical feasibility, safety, and favorable outcomes of MRI-guided stereotactic laser anterior corpus callosotomy in patients with LGS, making it a potentially safe and effective alternative to traditional open corpus callosotomy and other stereotactic methods including radiofrequency ablation and radiosurgery due to the ability to monitor the ablation in real time with MRI.

KEY WORDS: Corpus callosotomy, Drop attacks, Laser ablation, Lennox-Gastaut syndrome, Vagus nerve stimulation

Neurosurgery 85:E569–E574, 2019 DOI:10.1093/neuros/nyy273 www.neurosurgery-online.com

Lennox–Gastaut syndrome (LGS) is a severe epileptic encephalopathy characterized by polymorphic seizures and neuropsychological impairment.[1] Approximately 90% of patients have persistent disabling seizures despite the development of new generations of antiepileptic drugs (AEDs), nearly all have intellectual impairment and behavioral disturbance, and 5%-15% die prematurely.[2] Vagus nerve stimulation (VNS) and corpus callosotomy are effective palliative treatments for medically refractory LGS.[3] Emerging evidence has demonstrated the superiority of corpus callosotomy over VNS for seizure control, particularly for the disabling drop attacks.[4,5] Nevertheless, VNS is usually considered first because it is minimally invasive, reversible and does not carry the risk of complications associated with a craniotomy.[4] Here, we report for the first time a de novo successful anterior corpus callosotomy using minimally invasive stereotactic MRI-guided laser interstitial thermal therapy (LITT) in 2 patients with medically intractable LGS.

ABBREVIATIONS: AEDs, antiepileptic drugs; **GPFA,** generalized paroxysmal fast activity; **IRB,** Institutional Review Board; **LITT,** laser interstitial thermal therapy; **LGS,** Lennox–Gastaut syndrome; **MTLE,** mesial temporal lobe epilepsy; **VNS,** vagus nerve stimulation

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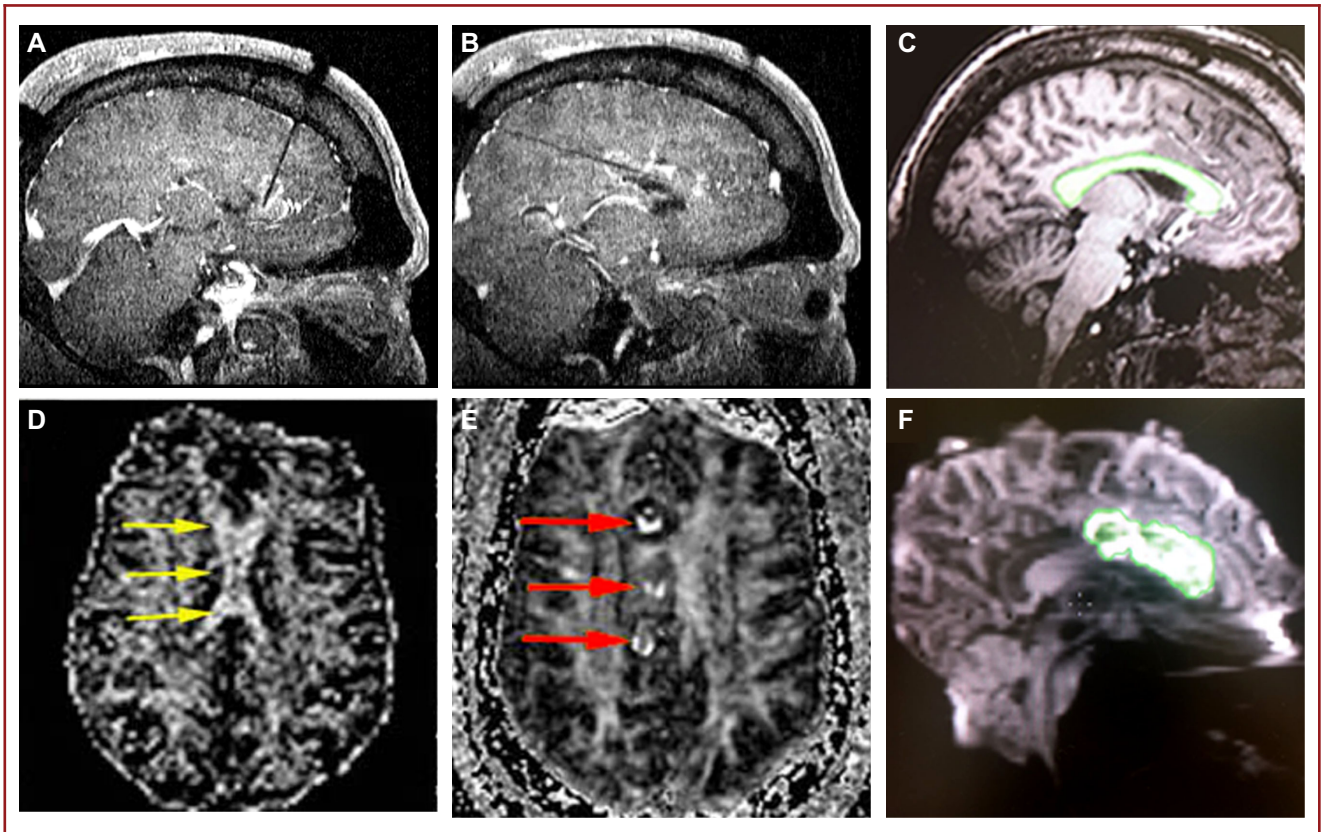


FIGURE 1. **A**, *Placement of laser fiber through a right precoronal frontal trajectory to ablate the genu of corpus callosum.* **B**, *Placement of a laser fiber through a right parietal trajectory along the longitudinal axis of corpus callosum to ablate the body of corpus callosum.* **C**, *Pre-ablation sagittal view of preablation corpus callosum on diffusion weighted MRI.* **D**, *Preablation diffusion weighted image at the level of body of corpus callosum. Yellow arrows indicated the intact corpus callosum.* **E**, *Postablation diffuse weighted image of the corpus callosum. Red arrows indicated the disrupted regions of corpus callosum, as compared to the same areas indicated by yellow arrows in D.* **F**, *Sagittal view of postablation volume on diffusion weighted MRI.*

CLINICAL PRESENTATION

Surgical Technique for MRI-Guided LITT

Patients were placed in a MRI compatible stereotactic head frame (CRW Integra Neurosciences, Plainsboro, New Jersey). A 1.0 mm-section stereotactic computed tomogram was obtained intraoperatively and subsequently fused with 1.0 mm-section volumetric gadolinium-enhanced T1- and T2-weighted MR images using Stealth software (Medtronic, Dublin, Ireland). Under general anesthesia, a laser optical fiber (Visualase system, Medtronic) was stereotactically implanted from a right frontal trajectory approximately with an entry point of 25 mm from midline and 26 mm anterior to the coronal suture in patient 1 and with the similar reference points 23 mm from midline and 24 mm anterior in patient 2 to target the anterior genu of the corpus callosum through a 3.2 mm twist drill perforation (Figure 1A). The target was in the midline anteriorly at the position of the anterior commissure and 4 mm above the roof of the third ventricle in both cases. Then, a second laser optical fiber was implanted using a parietal entry point and trajectory along the longitudinal axis of the corpus callosum to target the main body of the corpus callosum (Figure 1B). The entry point was 28 and 27 mm from the midline and 67 and 60 mm above the inion in the respective patients. The target for this trajectory was in the midline 4 mm above the roof of the third ventricle and 4 mm posterior to the anterior commissure. All surgeries were carried out in the half-sitting position. Patients were then transferred to a dedicated 3 Tesla MRI scanner (Philips, Amsterdam, The Netherlands) for MRI-guided thermal ablation after the position of the laser fibers was confirmed with another intraoperative CT in the stereotactic frame and refusion to the original planning MRI showing the calculated trajectory.[6] Temperature threshold was set at <50°C for pericallosal arteries to prevent off-target injuries.

Under real-time monitoring with MRI thermometry, the first lesion was generated via the frontal fiber in the anterior genu (**Video, Supplemental Digital Content 1**). A second lesion was generated in continuity with the first lesion via the parietal fiber.

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The parietal fiber was then withdrawn 1.0-2.0 cm caudally to generate a third in the body of the corpus callosum, and a fourth lesion was generated in patient 1 (**Video, Supplemental Digital Content 2**). Immediately after the procedure, a T1 weighted contrast-enhanced MRI image was performed showing a continuous lesion of the anterior corpus callosum congruent with the predicted damage zone in sagittal planes. Patients were subsequently treated with a 3-d taper of Dexamethasone to reduce postablative edema.

Volumetric Analysis of Ablation Volume

Volumetric assessment of ablation volume was performed by using stereotactic software (Stealth, Cranial Package, Medtronic). The complete corpus callosum was segmented first on contiguous sagittal T1-weighted slices (Figure 1C). The immediate postablation T1-weighted post contrast images were used to assess the lesion volume. The rim of contrast enhancement was drawn on these contiguous 1 mm slices and 3D-volumes calculated from interpolated thin slices. The volume of the disrupted callosal fibers was assessed using diffusion tensor weighted MRI (Figure 1D, E, and F).

Pre- and Postoperative EEG Recordings

Pre- and postoperative scalp video-EEG was recorded using Xltek EEG system (Natus Medical Incorporated, Pleasanton, California) according to the international 10-20 system with additional 6 sub-temporal electrodes (F9, T9, M1, F10, T10, and M2), and analyzed with high-pass filter of 1Hz, low-pass filter of 70 Hz, and sensitivity of 7 μV/mm. Rhythmicity spectrogram was calculated using Persyst software (Persyst, Solana Beach, California) for seizure detection.[7] The study was approved by the Institutional Review Board (IRB). Since the study was a retrospective analysis, IRB approval did not require direct acquisition of patient consent.

Case 1

A 40-yr-old, right-handed man with a history of significant developmental delay has had medically intractable LGS since early childhood. His seizures were mixed with tonic, atonic, myoclonic, and generalized tonic-clonic seizures. A vagus nerve stimulator (VNS) was implanted at the age of 27 yr with a modest improvement. At the time of surgical evaluation, he was having 3-5 convulsive seizures daily with 1-2 drop attacks despite being treated with 4 AEDs. His neurological examination revealed no focal deficits. Brain MRI showed no structural abnormalities. His EEG showed intermittent generalized 1.5-2.5 Hz slow spike-wave complexes and generalized paroxysmal fast activity (GPFA).

He underwent stereotactic laser anterior corpus callosotomy with 75% (53/71 mm) ablation of the anterior-posterior length and 80% (12.1/15.2 cc) ablation of the total volume of the corpus callosum (Figure 2). He was discharged 4 d after the surgery due to postoperative hypersomnia from which he completely recovered. A postoperative video-EEG study showed markedly reduced duration and frequency of GPFA and seizures compared to the preoperative video-EEG study. He has been free of disabling seizures including drop attacks for 18 mo of follow up. His attention and verbal output have also improved.

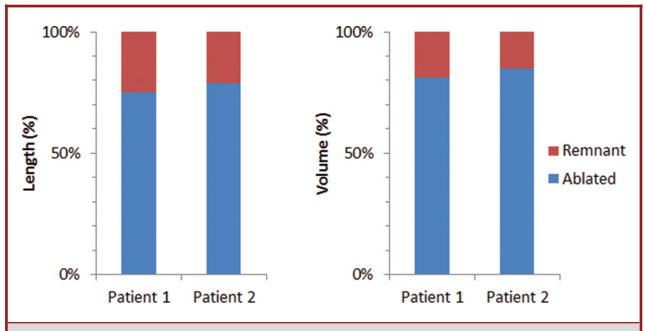


FIGURE 2. *Volumetric assessment of ablation in length and volume. The percentage of ablation in anterior to posterior length of the corpus callosum was 75% (53/71 mm) in patient 1 and 79% (60/76 mm) in patient 2. The percentage of total corpus callosum ablated volume was 80% (12.1/15.2 cc) in patient 1 and 85% (10.6/12.4 cc) in patient 2. mm: millimeter. Cc: cubic centimeter.*

Case 2

A 25-yr-old, right-handed man has Klinefelter's (XXY) syndrome, developmental delay and medically intractable LGS since 2 yr of age. His seizures include atypical absence, tonic, atonic, and generalized tonic-clonic seizures. A vagal nerve stimulator was implanted at 15 yr of age with minimal benefit. At the time of surgical evaluation, he was having 5-10 daily seizures and 3-5 drop attacks despite being treated with 4 AEDs. His neurological examination revealed no focal deficits. A brain MRI showed moderate diffuse atrophy. His EEG showed intermittent generalized 1.5-2.5 Hz spike and slow wave discharges and frequent GPFA.

He underwent the stereotactic laser anterior corpus callosotomy with 79% (60/76 mm) ablation of the anterior to posterior length and 85% (10.6/12.4 cc) ablation of the total volume of the corpus callosum (Figure 2). He was discharged 2 d after the surgery without complications. A postoperative video-EEG study showed markedly decreased epileptiform discharges compared to the preoperative video-EEG study, with the duration of GPFA reduced from 10-30 seconds to 1-5 seconds and more than 90% reduction in the frequency of GPFA (Figure 3). Clinically, he has had a more than 90% reduction of disabling seizures including drop attacks at 7 mo of follow up. He has become more alert and interactive with increased verbal output.

DISCUSSION

Traditional open corpus callosotomy carries a significant risk of surgical complications including subgaleal fluid collection and meningitis due to the dural opening; cerebral infarct and hemorrhage due to the damage to superior sagittal sinus,

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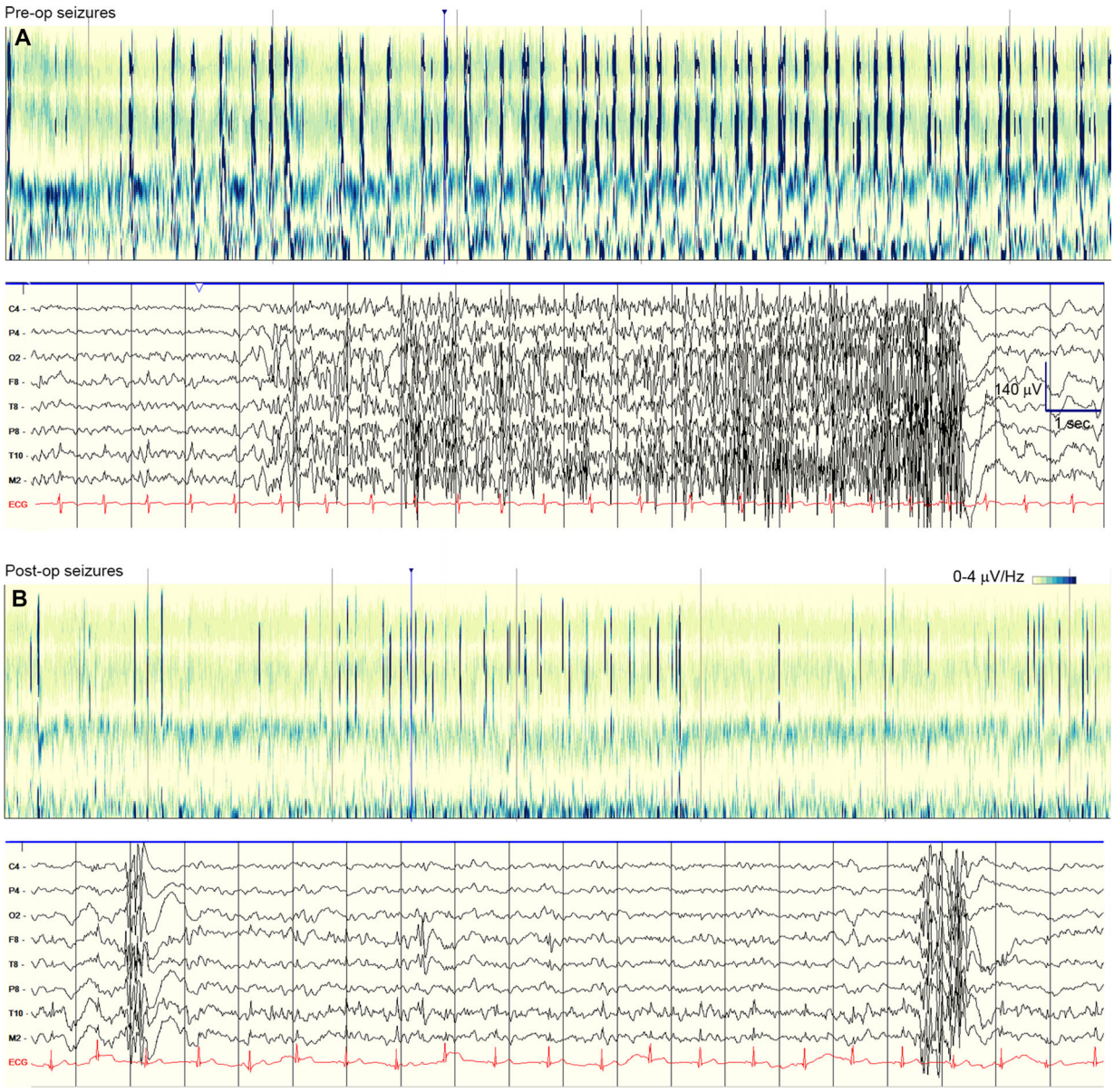


FIGURE 3. *The effect of interstitial laser callosotomy on seizure activity in patient 2.* **A**, *The rhythmicity spectrogram of the left hemisphere with frequent (~40) seizures during 1 h of sleep before the callosotomy is shown in the top panel. An example seizure is shown in the right hemisphere EEG leads; the seizure is marked with an arrow in the top panel.* **B**, *The rhythmicity spectrogram of the left hemisphere is shown in the top panel and shows markedly reduced epileptiform activities during 1 hour of sleep after the callosotomy. In the bottom panel, examples of epileptiform discharges are shown in the right hemisphere EEG leads; after the callosotomy, the brief epileptiform discharges were rarely manifesting motor activity on video-EEG. These generalized EEG epileptic patterns in this patient are displayed only in 1 hemisphere to reduce the size of the figure.*

callosomarginal, and pericallosal arteries through midline approach. Cognitive impairments and motor deficits may also occur due to the retraction or inadvertent injury of the cingulate gyrus and paracentral lobule.[4,8] Overall, the rate of complication for open corpus callosotomy can be as high as 21%, with 3.8% permanent.[9]

Minimally invasive techniques using endoscopic surgical technique and stereotactic radiosurgery have been performed to

reduce the risks of craniotomy.[10,11] Although the endoscopic technique is less invasive than traditional corpus callosotomy, it still requires a small frontal craniotomy and a microscopic interhemispheric approach.[10,12] Corpus callosotomy using radiosurgery has resulted in significant seizure reduction.[13] However, seizure improvement has a latency of 10 to 12 mo after radiation, and significant postradiation cerebral edema, headache, and radionecrosis with mass effect may occur. Additionally, the long-term side effects of ionizing radiation have to be taken into consideration, particular in children in the context of a comparatively benign disease.[14-16]

MRI-guided LITT is a promising new technique with several advantages including real-time monitoring of ablation volume with MRI thermometry, preventing off-target injury with temperature threshold, discrete lesion demarcation, and immediate efficacy.[17] Emerging evidence suggests that LITT might be a safe and effective alternative to traditional anterior temporal lobectomy in patients with mesial temporal lobe epilepsy due to its tolerability, reduced incidence of major complications, shorter recovery time, and decreased pain.[18-20] Sporadic cases of open laser corpus callosotomy have been reported previously. Carbon dioxide laser for corpus callosotomy using the OmniGuide system (OmniGuide, Lexington, Massachusetts) has been performed through a frontal craniotomy.[21,22] Interstitial stereotactic laser ablation of the splenium has been performed as a salvage procedure for patients who failed previous open anterior corpus callosotomy, and is therefore not a primary corpus callosotomy procedure.[23] A few laser corpus callosotomy cases were included in a study focusing on the complications of various procedures of LITT, however, operative technique and effectiveness were not clearly described.[24]

Here, we report 2 cases of de novo interstitial stereotactic laser anterior corpus callosotomy, demonstrating not only the operative technique, but also safety of LITT for patients with LGS. Favorable seizure outcomes were observed in both patients. Cognitive improvement was also observed clinically in both patients, although pre- and postoperative neuropsychological evaluations were not performed. Additional ablation, such as ablation of splenium to achieve a complete corpus callosotomy, at a later date could be considered if failure occurred, in contrast to the complexities of redo craniotomy. Likewise, a craniotomy could be offered at a later date if the LITT procedures failed to produce efficacy. The 2 patients in this report had medically intractable LGS with daily drop attacks and did not benefit from VNS therapy. Open corpus callostomy was recommended over the years and was not considered by either family. They subsequently opted for the minimally invasive LITT procedure. The procedure was well tolerated by both patients without complications. Postoperative pain after LITT was minimal compared to open craniotomy, and narcotics for pain control were not needed in both patients. Postoperative care in neurointensive care unit (NICU) was less than 24 h. Hospital length of stay was 2 d for 1 patient, and 4 d for the other due to a transient hypersomnolence.

CONCLUSION

These early data suggest that minimally invasive stereotactic laser anterior corpus callosotomy might be a safe and effective alternative to traditional open callosotomy and other stereotactic methods including radiofrequency ablation and radiosurgery due to the ability to monitor the ablation in real time with MRI. Nevertheless, the safety and efficacy of interstitial stereotactic laser anterior callosotomy cannot be critically assessed in this case report. LITT for epilepsy has a steep learning curve and this technique, although minimally invasive, requires long term experience to assess its potential benefits. Future prospective studies are warranted to determine its safety and efficacy as a potential first-line surgical treatment for patients with medically intractable LGS.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplemental digital content *is available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content 1. Video. This video showed the laser ablation of the genu of corpus callosum through a right frontal laser optical fiber.
Supplemental Digital Content 2. Video. This video showed the laser ablation of the body of corpus callosum through a right parietal laser optical fiber.

COMMENTS

Corpus callosotomy is a palliative surgical procedure that is appropriate for a selective group of patients with medically intractable epilepsy who are not considered optimal candidates for focal resective surgery. Historically, patients with Lennox-Gastaut syndrome, with frequent drop attack seizures, are considered to be the best candidates for this procedure. The rationale for this surgery is based on the hypothesis that the corpus callosum is a critical pathway for interhemispheric spread of epileptic activity and, consequently, responsible for the rapid synchronization of the epileptic discharges. The standard approach is through open midline craniotomies, careful dissection of the interhemispheric fissure and cingulate gyri and, finally, transection of the callosum fibers. Morbidity is relatively low, however, transient hemiparesis due to retraction of the mesial motor cortex is not a rare complication, and likely under-reported. In this manuscript, the authors reported 2 cases of anterior corpus callosotomy using MRI-guided stereotactic laser interstitial thermal therapy (LITT) as an alternative minimally invasive technique for alleviating the risks of craniotomies while achieving favorable outcomes. Larger series will likely consolidate and expand the utilization of this procedure in a highly challenging group of patients with highly debilitated seizures. I congratulate the authors for this work.

Jorge Gonzalez-Martinez
Cleveland, Ohio

This manuscript presents a novel way to treat one of the more difficult and dangerous problems related to LGS, atonic seizures or drop attacks. Historically, the treatment of choice is open craniotomy with corpus callosotomy. Although effective, the procedure carries high risk of perioperative morbidity. The authors suggest that using LITT to ablate the corpus callosum is a less invasive and safe technique. This manuscript is an important contribution to the LITT literature and shows how LITT is changing the landscape of management of intractable epilepsy by offering a less invasive technique, thereby minimizing postoperative pain, intensive care unit stay, and overall hospital stay. Likewise, LITT is expanding the use of surgical techniques for the management of intractable epilepsy by providing a more appealing surgical option to patients whom might otherwise forego open surgical intervention. The authors have achieved their primary goal of illustrating that corpus callosotomy can be done safely using current LITT techniques. One should use caution, however, when reading this manuscript as LITT techniques have a steep learning curve.

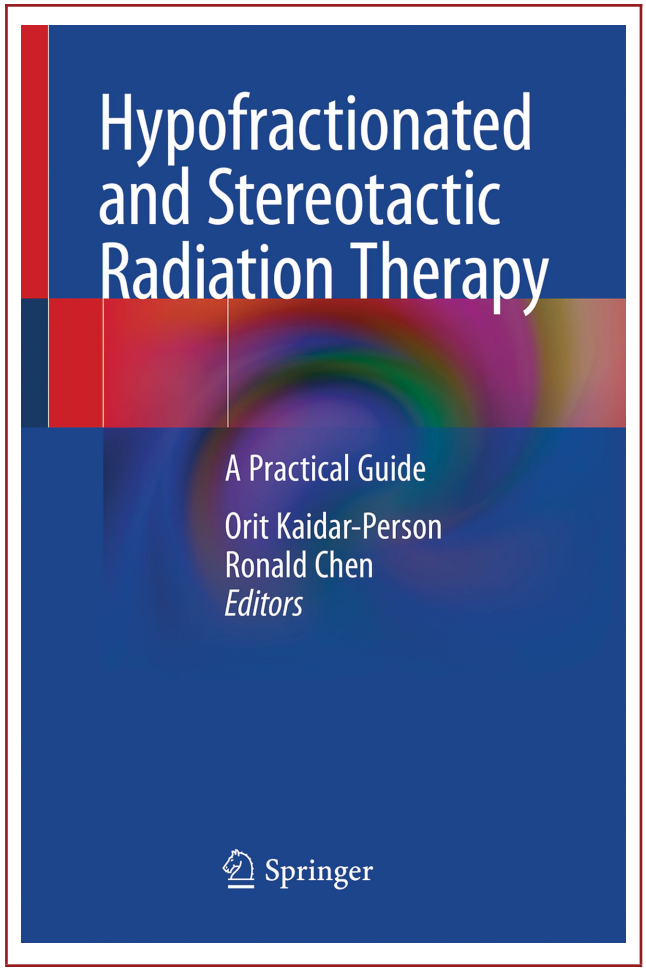
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Book Review: *Hypofractionated and Stereotactic Radiation Therapy: A Practical Guide*

By: Orit Kaidar-Person, Ronald Chen, editors
Published by: Springer International Publishing, AG, Cham, Switzerland, 2018
Softcover: 575 pp.
Price: $119.99
ISBN: 978-3-319-92800-5



Hypofractionated and Stereotactic Radiation Therapy: A Practical Guide succeeds in its titular goal, which is to provide a workable review of the utilities and logistics of hypofractionated radiotherapy. The authors should be commended for providing a comprehensive guide that covers critical topics such as common fractionation patterns, normal tissue toxicity constraints, and relevant literature. The chapter authors recruited by the editorial team to provide guidelines for hypofractionated radiotherapy are among the leaders of the field for their particular disease site.

The history of hypofractionated stereotactic radiotherapy is such that a review like the present publication is quite timely. While conventionally fractionated 3-dimensional radiotherapy and even intensity modulated radiotherapy has been practiced for multiple decades, hypofractionated stereotactic radiotherapy represents a more recent evolution within the field of radiation oncology. Moreover, since many of the risks of hypofractionated radiotherapy will occur at a delay of years after the treatment, the practice needed to be evaluated for several years before the true risks of toxicity can be estimated. In addition, the advents of stereotactic linear accelerators that have become widely available in the community make the presently reviewed text all the more timely.

Like most advances within radiation oncology, the practice of hypofractionated radiotherapy started with large academic centers, and has slowly disseminated to community practices. The author list is comprised of a diverse team of academicians whose practice has helped to establish the use of hypofractionation as an acceptable standard for its presently known indications. A supporting literature review is given for each indication for hypofractionation aged radiotherapy. A major strength of this publication is its tabular organization for critical topics such as relevant literature, treatment planning considerations, selection criteria for hypofractionation, and dose volume constraints. Indications for hypofractionation can vary based on tumor type. For malignant tumors, hypofractionation allows for potentially safer reirradiation. For benign tumors, hypofractionation may allow for decreased likelihood of treatment-related edema or cranial nerve injury.

The first chapter of the book reviews the history of hypofractionation in the context of historical fractionation schemes. The radiobiology of hypofractionated radiotherapy is also reviewed. The second chapter provides a medical physicist's point of view on the physics required for the safe and successful delivery of hypofractionated stereotactic radiotherapy. Among the clinical chapters covered in this book that would be of interest to a neurosurgeon or central nervous system (CNS) radiation oncologist include arteriovenous malformation, meningioma, vestibular schwannoma, glioblastoma multiforme, and brain metastases. A couple of topics of interest to neurosurgeons and CNS radiation oncologists that would be welcome in future editions include glomus tumors and skull base malignancies such as chordoma and chondrosarcoma.

A chapter of particular interest to neurosurgeons and radiation oncologists that treat CNS tumors is the chapter on spine tumors. This chapter reviews both primary spine tumors and spine metastases. The chapter includes a review of consensus clinical target volume contours for spinal metastasis treatment planning as well

as patient selection criteria for SBRT. Dose planning guidelines for both conventional linear accelerators and Cyberknife (Accuray) are included as suggested fractionation schemes. This chapter is as high yield and concise a review of spinal SBRT as there is available for the topic.

While the intended audience of this book is likely radiation oncologists, other subspecialitists such as neurosurgeons, neuro-oncologists, and medical oncologists may find this to be a useful reference. As a radiation oncology-specific text, it does include chapters that span the other disease sites that a radiation oncologist might use hypofractionated radiotherapy to treat. These include chapters on head and neck cancers, lung tumors, breast cancers, gastrointestinal malignancies, and gynecological malignancies.

A particularly helpful aspect of the organization of this book is the presentation of toxicity constraints for hypofractionated stereotactic radiotherapy from both QUANTEC and TG101, as well as an expert opinion recommendation for each indication for treatment. Providing multiple constraint sources are quite useful given the more recent implementation of hypofractionated radiotherapy compared to conventional fractionation regimens. A particular strength of the CNS chapters are guideline tables in which the authors describe target size constraints or other selection criteria in which hypofractionated radiotherapy is chosen over single fraction radiosurgery.

This book would be particularly helpful for radiation oncology residents in preparation for board examinations. Given the increasing usage of hypofractionation in a radiation oncologist's armamentarium, trainees must be able to demonstrate a competency with the indications, limitations, and safety constraints of this technology. Delivery of fewer fractions translates into a greater risk to patients if delivery is inappropriate. As such, hypofractionation has become a favorite topic of examiners in the field of radiation oncology. Moreover, knowing the strength of the data in support of hypofractionation is also a must. This book certainly is organized well for trainees wishing to use it as a study guide for the practice of hypofractionated radiotherapy.

In summary, this book is an excellent review of the literature supporting the usage of hypofractionated radiotherapy. It is well organized and presents in tabular format important indications for hypofractionated radiotherapy. Of the readership of Neurosurgery, CNS radiation oncologists, brain and spine tumor neurosurgeons, and radiation oncology residents would particularly benefit from the expertise provided in this review. Community radiation oncologists would also find this review quite useful given the relative novelty of hypofractionated radiotherapy and how there are fractionation schemes and dose volume tolerances well spelled out.

Disclosures

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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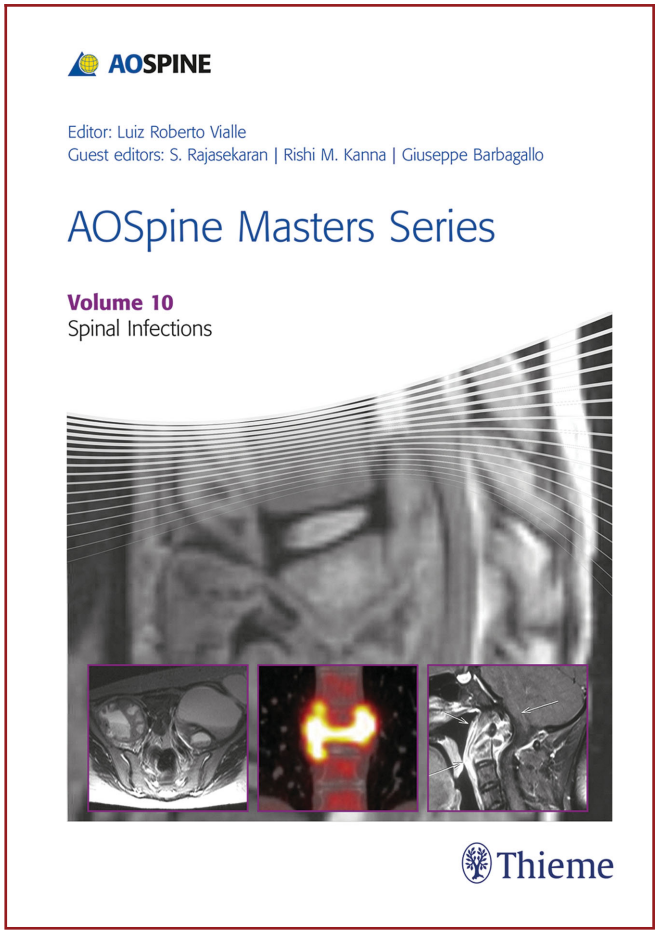
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Book Review: *AOSpine Masters Series, Volume 10: Spinal Infections*

By: Luiz Roberto Vialle, S. Rajasekaran, Rishi M. Kanna, Giuseppe Barbagallo, editors
Published by: Thieme Medical Publishers, Inc., New York, New York, 2018
Hardcover: 577 pp.
Price: $119.99
ISBN: 9781626234550



Spinal infections can be one of the most difficult spinal conditions to diagnose and treat. Should the 68-yr-old woman with end stage renal disease with L4/5 spondylodiskitis be surgically treated because of worsening magnetic resonance imaging findings after 6 wk of antimicrobial therapy? Does hardware use in spine surgery change outcomes? How does tuberculosis (TB) lead to deformity in the pediatric population? These are just a sliver of the complex questions addressed in this text. Spondylodiskitis requires a holistic and multidisciplinary approach to patient care. Being an excellent technician is not enough to adequately care for this patient population. One must be able to interpret image findings, address medical comorbidities, and know when antimicrobial therapy alone is sufficient. It is just as important to know when antibiotic therapy alone is insufficient and surgery must be pursued. This text synthesizes what is currently understood about the epidemiology, microbiology, and radiography of various spinal infections. In addition, it reviews the indications for both surgical and nonsurgical treatment.

The first 7 chapters of the text focus on pyogenic spinal infections. Specifically, it reviews the epidemiology, microbiology, radiographic findings, and clinical features. One of my favorite sections in this group was chapter 2 where the authors reviewed the potential risk factors and preventative strategies for surgical site infections. They also reviewed the vascular anatomy of the spine. Having this basic understanding of how anatomic realities ultimately drive pathology is imperative to understand the location of infections, why image findings progress in a certain way, and whether surgery will ultimately be necessary. Pathophysiology, among other topics, is reviewed in chapters 1 and 5. Since the response to antimicrobial therapy can be ambiguous, it is important to be able to interpret the clinic picture, laboratory results, and image findings. Chapter 3 discusses the image findings that help guide diagnosis as well as treatment response. Chapters 6 and 7 review the conservative and surgical treatment for pyogenic spondylodiskitis and spinal epidural abscesses, respectively.

Chapters 8 to 10 focus specifically on TB. Seeing as how I am from the United States this section has a historical feel since TB in the US is so well controlled. Any spine surgeon in the US today will have very limited exposure to TB of the spine. In 2017, there were only 9105 new cases of TB reported in the US according to the Center for Disease Control. Unfortunately, TB continues to be one of the leading infectious disease killers globally with an estimated 10 million new TB cases worldwide in 2017 alone. Seeing as how many of this text's authors live in areas of the world where TB is a very real threat there is no doubt that they are experts on this topic. In these chapters, we review the epidemiology, clinical features, pathogenesis, diagnosis, and treatment options for spinal TB. There is a full chapter dedicated to discussing drug therapy for spinal TB, chapter 9. What I liked most about this chapter was going over the history of drug treatment for TB and how that history has impacted our current understanding. We also learn about multidrug-resistant TB as well as extensively drug-resistant TB (a term I had not heard of before). Finally, all of chapter 10 is dedicated to the surgical management of TB and reviews such important topics as indications, approach, instrumentation, and deformity correction.

Next, chapters 11 and 12 focus on pediatric spinal infections and infections at the craniocervical junction.

The rest of the text, chapters 13 to 18 focus on the relation of spinal infections to specific populations. These topics include minimally invasive surgery, HIV, postoperative state, peri-implant infections, geriatric patients, and pseudoarthrosis.

Spinal infections are a multidisciplinary problem that can be difficult to diagnose and treat. When I am met by a complex case, I frequently find myself trying to decide whether the infection has cleared or if a debridement is needed. There are many factors that go into this decision-making process including: location, age, comorbidities, microbiology, duration of treatment, clinical picture, laboratory results, image findings, drug sensitivities, etc. Unfortunately, in medicine, no 2 patients are alike and there is a multitude of permutations that must be taken into account when making a final decision on treatment. Having an in-depth understanding of this disease process from this text will help guide that decision-making process. Anyone in the medical field who treats patients with spinal infections would be well served by this textbook.

Disclosures

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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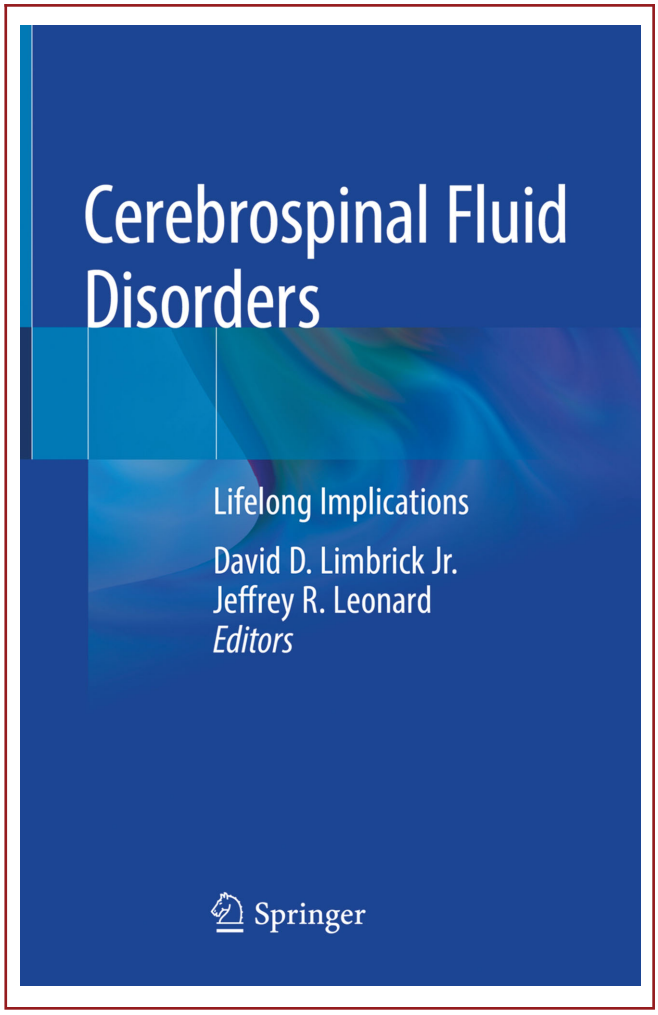
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Book Review: *Cerebrospinal Fluid Disorders: Lifelong Implications*

By: David Limbrick, Jeffrey Leonard, editors
Published by: Springer International Publishing AG, Cham, Switzerland, 2019
Hardcover: 579 pp.
Price: $159.99
ISBN: 978-3-319-97927-4



The book *Cerebrospinal Fluid Disorders: Lifelong Implications* edited by David Limbrick and Jeffrey Leonard comprises a collection of selected research efforts in hydrocephalus. It is substantiated by authors known as experts as well as pioneers in the field of clinical and experimental research.

While the selected topics do not entirely cover the full research spectrum of hydrocephalus and associated cerebrospinal fluid (CSF) disorders, the book's contributions cover the most important aspects of contemporary and current "state-of-the-field" research and provide detailed and profound insights into novel methods and promising techniques in the diagnosis and management of hydrocephalus, neuroimaging, biomechanical biomarkers, and genetic disease mechanisms and their effects on the nervous system.

The concept of introducing hydrocephalus and CSF disorders as conditions that occur across the lifespan is a very promising one. The important message of this book is that hydrocephalus is indeed the "posterchild" of a lifelong threat to one's health (ie, adult-onset congenital hydrocephalus such as LIAS and LOVA), and even in the experienced hands, treatment of hydrocephalus remains challenging and baffling (ie, multiloculated hydrocephalus and "ex-vacuo" hydrocephalus). Yet, hydrocephalus is often belittled and considered trivial.

Considering the concept of the book, I would like to briefly discuss the contributions important to my research and the "take-home message."

Anatomy and Physiology-Based Magnetic Resonance Imaging in Hydrocephalus by Smruti K. Patel et al

This article nicely shows the distinct roles of magnetic resonance imaging (MRI) techniques to provide anatomical (ie, CISS, FIESTA), quantitative, and qualitative (ie, TIME slip) measures of CSF anatomy, physiology, and flow. In daily routine and health care, the contribution and value of MRI data is still under-recognized. MRI not only has the potential for enterprising the CSF physiology, but also has the potential for addressing the metabolic aspects of brain function in hydrocephalus (ie, DTI HUBS to study brain connectivity). The article makes a strong argument for utilizing more comprehensive MRI studies and prospective MRI protocols before and after shunting in hydrocephalus to prove the MRI as a sensitive and specific biomarker. This contribution implies short-term success to the MRI's potential for assisting the future routine diagnosis and surgical management of hydrocephalus.

Cerebrospinal Fluid Biomarkers of Hydrocephalus by Albert M. Isaacs and David Limbrick

While CSF biomarker research has mushroomed over the past few decades, research work on hydrocephalus has dropped due to the lack of definitive clinical implications. Isaacs et al provide an honest but more so very thorough overview of CSF biomarker studies. The 9-page evidentiary table is exceptional and unique and elegantly summarizes the CSF biomarker findings across hydrocephalus etiologies: congenital, acquired,

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from infancy through adulthood and idiopathic normal-pressure hydrocephalus. CSF biomarkers in hydrocephalus rather reflect the multiple and heterogeneous "injuries" to the brain based on etiology and/or the underlying pathological process (ie, axonal damage, ischemia, inflammation, etc), each leaving a different "footprint," making it improbable to isolate a single biomarker. Also, another major challenge is the lack of true controls. The authors recommend cross-validation approaches, ie, genomic analysis, to validate the proteomic findings and to put this on a broader scale utilizing multicenter CSF repositories such as that maintained by the Hydrocephalus Clinical Research Network. This chapter provides a helpful guide to future biomarker research and encourages pursuing research in this field, given the existing bulk of findings.

Physiology of Foetal Onset Hydrocephalus by Esteban Rodriguez et al

Congenital Hydrocephalus by Charuta Gavankar Furey et al

Genetics of Hydrocephalus: Causal and Contributory Factors by Hannah Tully et al

It is mind blowing that experimental work has identified hundreds of genes potentially involved in hydrocephalus etiology. However, clinical research in this field has identified just 12 genes in human patients. Overall, studies so far imply that in severe hydrocephalus of prenatal or early onset, otherwise unexplained, genetic testing of the offspring and family is warranted. The articles suggest that genetic testing more rigorously and standardly applied in patients with hydrocephalus, across lifespan, of anything, has the greatest potential for changing the research and clinical management of hydrocephalus.

Even though the above articles also bring up the subject of future treatment of hydrocephalus to include pharmacological engineering (ie, stem-cell treatment) of the CSF, it is clear that this is experimental and far from clinical applications.

Endoscopic Third Ventriculostomy With Choroid Plexus Cauterization (ETV/CPC) Versus CSF Shunting by William B. Lo and Abhaya V. Kulkarni

The historical overview of choroid plexus cauterization (CPC) is very educational, and reminds us of its roots in light of Warf and colleagues, who have pioneered the modern concept of endoscopic third ventriculostomy (ETV) combined with CPC. This article gives an honest statement about the still-unexplained differences between the Africa and US long-term efficiency of ETV/CPS, which are speculated to lie in the different pathologies treated (high prevalence of postinfectious hydrocephalus in Africa). It is also stated that so far ETV/CPC has not reached the standard of treatment, and that there remains clinical equipoise. Prospective trials are on the way, and that is important information provided by the Hydrocephalus Clinical Research Network.

Cerebrospinal Fluid Shunting by William Whitehead

This contribution admits to the fact that the evaluation of long-term neuropsychological outcomes is increasingly important in the field of hydrocephalus when comparing treatment options such as endoscopic ventriculostomy alone, endoscopic third ventriculostomy with CPC and CSF shunting. It is sobering that even to date shunting has not shown any effect on brain development or metabolism in the maturing brain despite multiple neurocognitive tools available.

Randomized Clinical Trials in Pediatric Hydrocephalus by Evan J. Joyce et al

Technical Advances in the Treatment of Hydrocephalus: Current and Future State by Hauptman et al

The synopsis on the randomized clinical trials is also important as it becomes clear that prospective trials are mainly aiming to improve surgical techniques, to minimize complications, and to improve long-term survival of shunts. None of the trials thought of looking at what is also a pressing matter, the cognitive, metabolic, and pharmacological outcome of hydrocephalus, as pointed out by the earlier chapters in the book. It becomes evident that here is still a whole alley to improve surgical techniques; however, there exists a challenging collaboration between physicians and engineers and the lack of rigorous prospective design of protocols.

In summary, this book advocates for hydrocephalus. We are still facing a significant morbidity and mortality with a 5-yr survival of treated hydrocephalus of little above 30%. This has been a stagnant figure since decades. This is the more disappointing when considering the great treatment results in pediatric cancer, which have arisen to a curable prospectus.

In this regard, *Cerebrospinal Fluid Disorders: Lifelong Implications* allows an important, in-depth insight and knowledge extraction for physicians as well as researchers interested in specific aspects of hydrocephalus research and treatment along with guidance to future research and its potential impact on the health care system.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

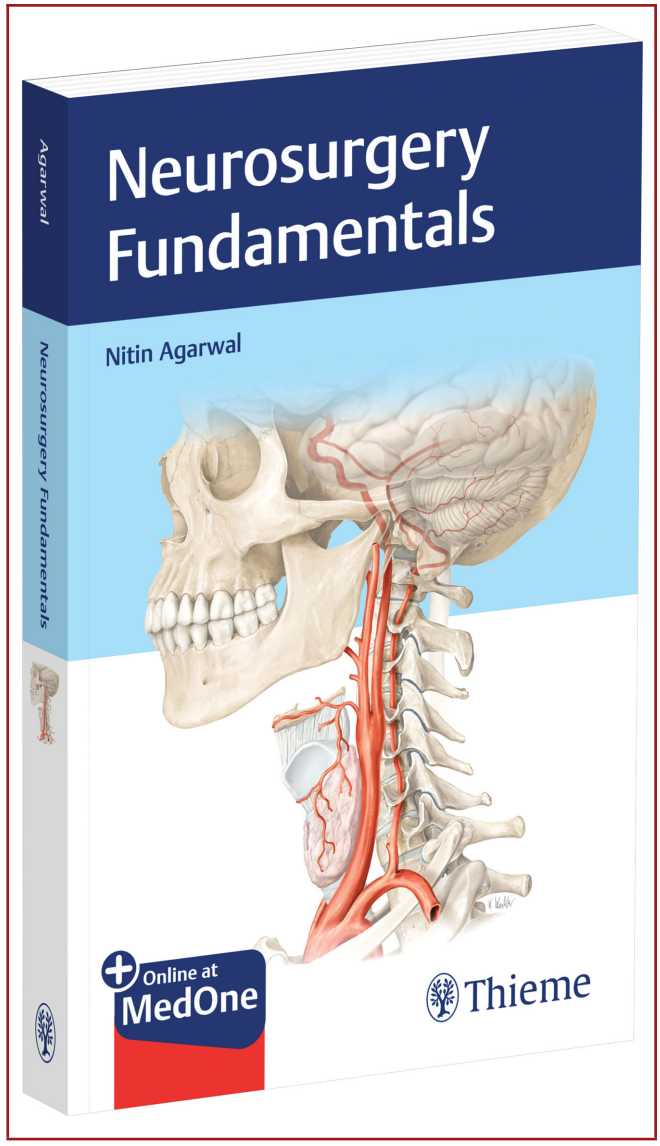
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10.1093/neuros/nyz252

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Book Review: *Neurosurgery Fundamentals*

By: Nitin Agarwal, editor
Published by: Thieme Medical Publishers, Inc., New York, New York, 2018
Softcover: 581 pp.
Price: $39.99
ISBN: 9781626238220



Authoring a comprehensive textbook across any medical discipline is a formidable task, not only due to the need for consolidating a large amount of information, but also because making such texts immediately accessible and practically useful is often easier said than done. The neurosurgery literature has seen a number of contributions of this type, varying from the "office desk" format of Youmans and Winn.[1] to the "white coat pocket" style of Greenberg,[2] which have remained relevant by being up to date and always applicable to the ever-expanding repertoire of the modern neurosurgeon. For these and other volumes, similar challenges crop up with every new release: Which topics should be included and discarded? To whom is this book targeted? Where do the authors find the best evidence? How authors answer these questions contribute to their volumes' usefulness, and their longevity on the bookshelves of neurosurgery practitioners and trainees.

Neurosurgery Fundamentals (ed. Nitin Agarwal, Thieme, 2018) is another recent book aiming to provide an overview of the specialty, but in contrast to many other "handbooks" of neurosurgery, there seems to be a focus on the novice surgeon. In addition to a review of practical medical knowledge and decision points across all neurosurgical subspecialties, there are practical beginners' tips such as operating room behavior and a neuroanatomy review, as well as commentary on adjacent fields such as infectious disease and neurocritical care. Most notable are probably the bookend chapters, focused on the career development within neurosurgery, in particular the match process and life after residency. It seems the authors endeavored to create a "start to finish" guidebook for neurosurgery, something that trainees can put in their pockets on the first day of medical school and pass on to others after signing their first job. This approach is novel for handbooks of this type, and the authors are to be commended for bringing attention to underappreciated teaching points in our field.

The book is divided into 20 sections covering the breadth of neurosurgical topics. The bulk is composed of a review of subspecialties. Each chapter begins with an introduction to the anatomy and pathology in question and includes imaging, clinical diagnosis, and nonsurgical treatment. Discussion of surgical treatments is focused on procedural selection the pros and cons of various treatment modalities, rather than surgical technique. In general, the authors discuss the evidence around each decision point and any applicable guidelines. For instance, in discussing aneurysm treatment, the authors review the historical development of both clip ligation and coil embolization, with a review of the International Subarachnoid Aneurysm Trial and BRAT data relevant to surgical decision-making. There is a measured review of other endovascular options as well. The Neurosurgical Oncology chapter is understandably broad, including the variety of brain tumors as well as a brief discussion of pathology and molecular biology in some cases. That there is little discussion

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of glioma molecular subtyping (eg, 1p19q codeletions, 06-methylguanine-DNA methyltransferase methylation status, etc.) is odd, particularly given their emphasis in the latest World Health Organization central nervous system tumor guidelines. The chapter on Movement Disorders, unlike in many similar books, includes surgical indications for various ablative or stimulation procedures and a discussion of the evidence behind each. There is a remarkably thorough and helpful discussion of presurgical evaluation of epilepsy, a workup usually missed by many residents before the patient arrives in the operating room.

Each section ends with "Top Hits," a short series of questions addressing relevant key points from the chapter. For the most part, these questions hit major learning points that can be used to assess self-learning but are sometimes overly granular and of questionable practical utility (eg, the anatomy of the Artery of Percheron). Some chapters include helpful knowledge pearls as well. There are sometimes details that seem to be included for completeness but have questionable clinical usefulness, such as a table of primitive neurological reflexes or a discussion of the anatomy of Rexed's laminae: these seem to be more relevant to a written board examination review book than the other, more clinically focused tidbits. Throughout these sections, images and figures are of high quality and quite illustrative, although one wishes that more surgical anatomy or intraoperative pictures would be considered.

The strongest material in the book is in the discussion of essential neurosurgical skills for beginners, which should be essential reading for all medical students seriously considering neurosurgery or completing a neurosurgery sub-internship, as well as other providers just beginning to understand neurosurgical patients and procedures. The section on the Neurological Examination is appropriately thorough and even includes a discussion of accessory maneuvers such as FABER test and bulbocavernosus reflex which are essential to neurosurgical practice. The "Clinical Scenarios" subsection of the Neuroradiology chapter is a useful way to review the normal anatomy illustrated earlier in the chapter and offer the kind of "quick hit" pathology/radiology/treatment bullets that can be reviewed on the fly. The Operating Room chapter is a bevy of immediately useful information; all major cranial and spinal approaches are reviewed with relevant anatomical concerns, as are patient positions and common resulting complications. Many of the "positioning" sections actually describe the procedure in full, and this text might be more appropriate in the dedicated Vascular, Oncology, or Spine chapters. The discussion of operating room etiquette is a small but very worthy addition, as this is often the thing most noticed about early trainees in the operating room.

Finally, there is the unique inclusion of the "career-oriented" sections of the book, which are quite rare to find. The first is a Roadmap to a Career in Neurosurgery, wherein the authors review the statistics of recent matched applicants in neurosurgery and discuss some of the statistics behind successful matches. The authors deserve credit for 3 important items. First, for using concrete data from the National Resident Matching Program and recently published papers on neurosurgical education to make their points, rather than off-the-cuff advice that can often be biased or incorrect. Second, for offering practical advice to medical students getting involved early in neurosurgery and all the way through their residency interview. And third, for specifically addressing the concerns of international medical graduates, who are an increasingly larger part of the applicant pool and often neglected. The profiles at the end of this chapter are charming anecdotes from well-respected practitioners, but are of questionable utility in terms of attaining a residency position. The Advice from the Masters section is mostly a compendium of available resources for neurosurgical studies, and while it is good to see them compiled and targeted for early trainees, the actual "advice" is a few short stories shuffled to the end of the chapter. The stories are, however, full of insights that are hard-earned and should be heeded by all aspiring neurosurgeons.

The goal of books such as *Fundamentals* is to start trainees down a path to understanding, to lay out the essentials of a given subfield to generate interest and questions that can be fulfilled by more detailed reading, and the authors succeed in accomplishing this. At the same time, they seem to want this volume to be a handbook reference for all trainees. All the material is of high quality and is quite insightful in terms of what content trainees should cover. But the question remains: for whom is this book written? While medical students on rotation will benefit from the early chapters, more advanced material such as tumor genetics, pathological stains, complex vascular anatomy, and the particulars of deep brain stimulation are less useful for student rotations, and if needed there are other introductory books that cover these topics more convincingly. Junior residents using this book might find it difficult to locate the algorithms, anatomical references, and clinical decision points with the immediacy their job often requires. Senior residents and attendings would likely turn to more advanced texts for a nuanced discussion.

The idea to make a catch-all guidebook for navigating a neurosurgical career is an absolutely essential one, and deserves even more text that it has been allotted in this volume; these concepts are so often held in secret among neurosurgeons as "members of the club," and sharing them would benefit us all. Future editions of this book could benefit from a more focused approach. If this is meant for medical students, junior residents, and advanced practice providers, include what exactly they need to know, from the career decision making process to the clinical knowledge that can enable them to be effective and efficient team members. If meant for more senior residents, then perhaps a renewed focus on job- and fellowship-finding is in order. Doing so would help make the book more immediately accessible and differentiate it from other neurosurgical handbooks. Still, the authors are to be praised for trying something quite new here: making a guidebook for the "whole surgeon" and addressing as many of his/her concerns *around* neurosurgery as *within* neurosurgery. Residency training is

perhaps one of the most transformative experiences in a surgeon's life, and having a book to help navigate it would be an invaluable resource. *Neurosurgery Fundamentals* is a key step toward a cogent introduction to the practice of neurosurgery, and with some refinement, should become required reading for everyone aspiring to join our most intriguing of surgical specialties.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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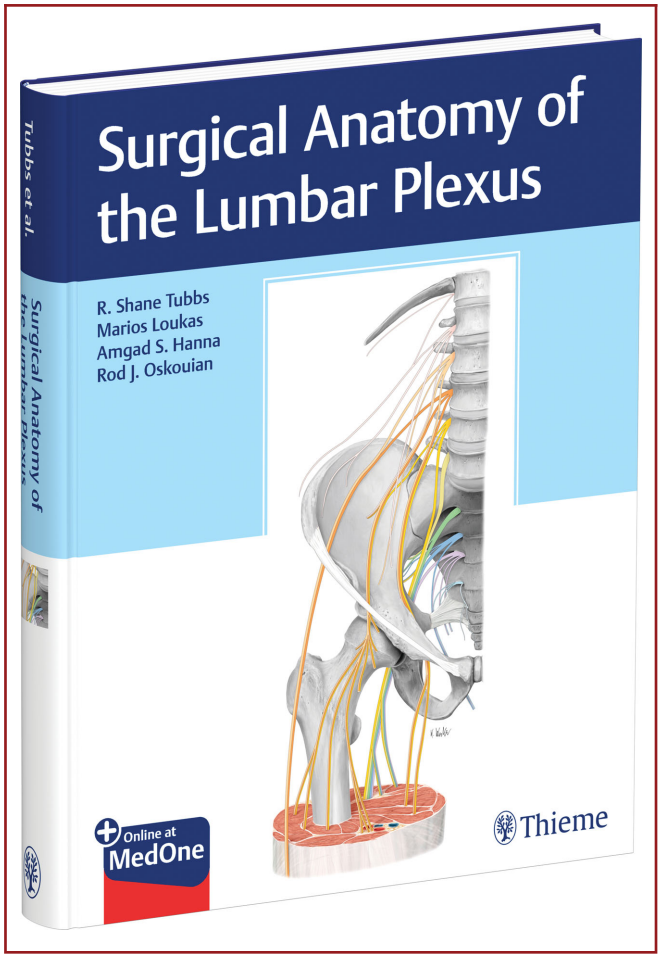
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Book Review: *Surgical Anatomy of the Lumbar Plexus*

By: R. Shane Tubbs, Marios Loukas, Amgad S. Hanna, Rod J. Oskouian, editors
Published by: Thieme Medical Publishers Inc, New York, New York 2018
Hardcover: 584 pp.
Price: $99.99
ISBN: 9781626238893



It was a pleasure to read and review *Surgical Anatomy of the Lumbar Plexus*. This book maintains a long tradition of surgical anatomy books. Historically, surgeons have always contributed to the advancement of the knowledge of anatomy. This book follows and honors this long-standing tradition.

The subject of lumbar plexus has been lacking a proper surgical anatomy text, and this book came to fill this void. The book is a brainchild of neurosurgeons and researchers at the Swedish Neurosciences Institute in Seattle, but it lists 43 chapter contributors from many departments around the world, including authors not only with a medical or neurosurgical background, but also from basic science departments such as anatomy and physiology. The latter contributors provide an interesting and important addition to a book dedicated to surgical anatomy because they add their knowledge to subjects such as anatomical variation (chapter 11) and to the comparative anatomy of the lumbar plexus (chapter 47).

The book consists of 27 chapters structured as follows. After a chapter with an initial surgical anatomical overview of the lumbar plexus, there are another 9 surgical anatomy chapters describing the lumbar plexus nerves. These chapters are consistently structured, with subsections presenting the anatomy, the pathology, and the clinical and surgical aspects of these nerves. A chapter describing the anatomical variation of the lumbar plexus follows. Subsequent chapters are distributed as follows: chapter 19 on the subject of "Lumbar Dorsal Root Ganglia," chapter 25 on "Microanatomy of the Lumbar Plexus," and then other chapters in the following order: a chapter on the imaging of the lumbar plexus, followed by another chapter on the anatomical pathology of lumbar plexus, and one describing iatrogenic lesions of the lumbar plexus following surgical procedures. Four chapters (15-18) have content describing more detailed surgical approaches to the lumbar plexus. Chapters 20 and 21 are focused on historical aspects of dermatomes, while chapters 22 to 24 are focused on describing anesthetic blockade techniques. These chapters are followed by a chapter on microanatomy; however, it is important to mention that the microanatomy term used in this book has not the meaning of microsurgical anatomy but a chapter on histology. The last 2 chapters are on surgical anatomy and external body landmarks and, finally, a chapter on the comparative anatomy of the lumber plexus.

Most chapters are very well illustrated with figures with the exception of 2 chapters: the one on comparative anatomy, which has only tables but no figures, and, strangely, also chapter 15, a short chapter on lumbar plexus anatomy with application to lateral approaches to the lumbar spine. The figures include traditional anatomical atlases, artistic atlases, illustrations, anatomical dissections, neuroimaging figures, and histological cuts. One comment that can be made is that with the exception of the histological figures, most figures are small, in particular the very good dissections presented in the surgical anatomy chapters. I would rather have, for example, for these anatomical dissections, larger figures to facilitate the appreciation of the lumbar plexus by the reader. Also, some of the cadaveric dissection figures lack a clearer identification of the structures surrounding the nerves. The text itself in all the chapters is appropriate for the subject discussed, and although the book

is multiauthored, the editors did a very good job in evening out the level of depth of all the manuscripts received for the chapters.

The book, albeit its title, also aims at a readership outside the field of neurosurgeons, spine surgeons, plastic surgeons, and peripheral nerve surgeons. The inclusion in the book of chapters describing anesthetic techniques indicates that anesthesiologists are also targeted for the purposed readership. Moreover, the book may find readers among allied health practitioners such as nurse practitioners and physical therapists; some of the chapters might be very useful for these fields. The subject of the book itself is the lumbar plexus, and possibly a better title for this book would be clinical and surgical anatomy of the lumbar plexus since there is much information in it that it is not per se surgically relevant. Still, the book is a very important addition, as the first book dedicated to the education of the surgical anatomy of the lumbar plexus. Because of the amount of work required for the publication of such a book, the authors are commended by presenting a very comprehensive opus on this neglected subject.

Overall, this is a very good book, and it is recommended in the armamentarium of those who manage pathologies and the reconstruction of the lumbar plexus. It will be an important resource for those operating at this anatomical region.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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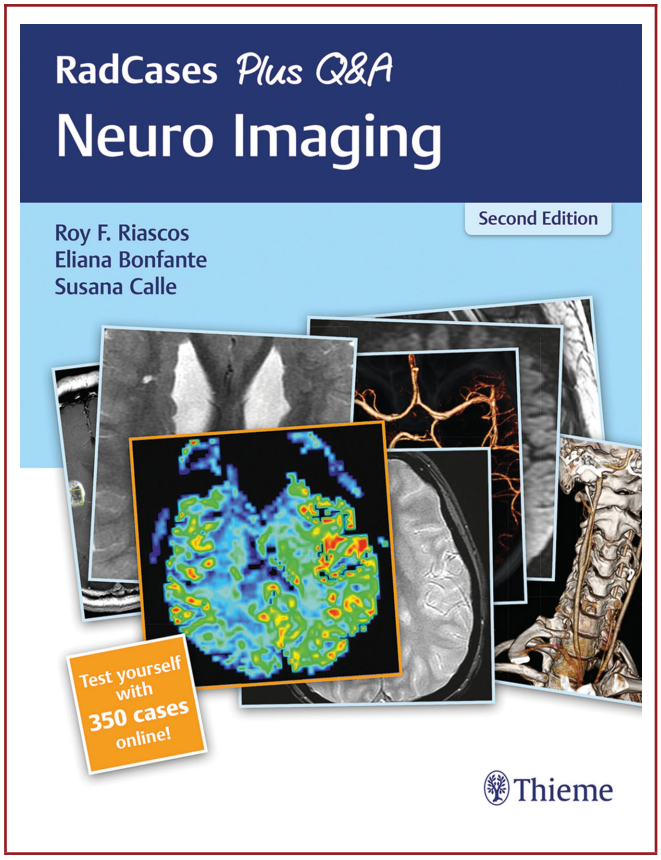
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Book Review: *RadCases Plus Q&A: Neuro Imaging*, Second Edition

By: Roy F. Riascos, Eliana Bonfante, Susana Calle, editors
Published by: Thieme Medical Publishers Inc,
New York, New York 2018
Paperback: 586 pp.
Price: $69.99
ISBN: 9781626232372



This 252-page book authored by Dr Roy F. Riascos, Dr Eliana Bonfante, and Dr Susana Calle uses a case-based format to cover a wide range of clinical concepts and diagnoses in neuroradiology in a succinct and effective manner.

In this second edition, the authors expand upon concepts introduced in the first edition by providing updated diagnostic and management approaches, as well as by introducing new pathological entities. New features include a question-and-answer section designed to reinforce important concepts, as well as access to an interactive electronic database that contains 250 additional cases to go along with an electronic version of all cases from the printed book.

The book is composed of 100 carefully chosen cases, which cover essential common clinical diagnoses in neuroradiology, as well as some less common but still important entities. Each case is presented as a short clinical vignette accompanied by a series of high-quality images, followed by a brief description of the relevant imaging findings alongside annotated images. A targeted differential diagnosis is then presented with a brief description of each clinical entity, followed by a "pearls and pitfalls" section that highlights key takeaways.

A wide variety of clinical disease categories and concepts are covered, including congenital, vascular, neoplastic, toxic-metabolic, trauma, and autoimmune. Multiple cases from each disease category provide readers with a comprehensive yet focused review. For example, a review of infectious diseases includes cases of common spinal infections (bacterial spondylodiskitis, spinal epidural abscess) and intracranial infections (cerebral septic emboli, pyogenic meningitis, fungal meningitis, cerebral abscess, etc), as well as a detailed discussion of AIDS dementia complex and infectious diseases affecting immunocompromised patients.

For trainees in their radiology residency, as well as those in neurosurgery and neurology, this book provides an excellent introduction to neuroradiology. Physicians who are already in practice but would like a quick easy-to-read reference or an updated overview of neuroradiology would also find this book helpful. This is a concise and practical resource.

As expected with any attempt to cover a broad topic in a concise review book, not all clinical entities can be included. However, one of the areas that I thought could be expanded upon was stroke imaging. Specifically, case 36 discussed intracranial large vessel occlusion in the context of grading leptomeningeal collaterals as a prognostic factor for patient outcome following intra-arterial thrombectomy. Given recent advances in stroke imaging and stroke treatment over the past 5 yr, I think this would have been a good opportunity to discuss CT perfusion and its prognostic role as well as its role in guiding the treatment for patients with large vessel occlusion. However, this is by no means a critical shortfall of the book, as, overall, the authors did a wonderful job of providing a comprehensive review of neuroradiology.

While each individual case included an appropriate number of high-quality images, many of the annotated images were small in size. This made it more challenging to appreciate pertinent imaging findings on the annotated images. Perhaps text could be reduced in select cases, to allow for larger images.

Overall, the authors did an amazing job covering the common pathologies and fundamental concepts of neuro-radiology, and I would highly recommend this book to

anyone looking for an easy-to-read comprehensive review of neuroradiology.

Disclosures

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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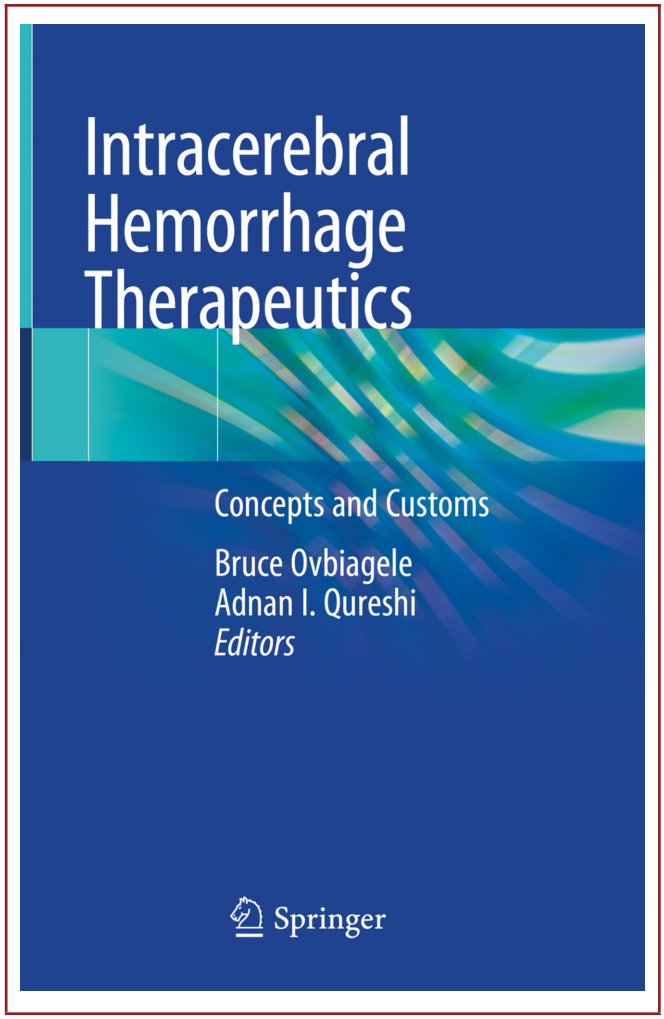
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Book Review: *Intracerebral Hemorrhage Therapeutics: Concepts and Customs*

By: Bruce Ovbiagele, Adnan I. Qureshi, editors
Published by: Springer International Publishing AG, Cham, Switzerland 2018
Hardcover: 588 pp.
Price: $149.99
ISBN: 978-3-319-77062-8



The editors present a 12 chapter book compiling the basic tenets for evaluation, management, and prognostication of patients with spontaneous primary intracerebral hemorrhage (ICH). The book is intended for primary care physicians, emergency medicine specialists, neurologists, and most subspecialists who participate in the care of these complex patients. The contributors represent a long list of accomplished experts in the field across multiple disciplines and the chapters follow the continuum of care for these patients from the prehospital and emergency department stage to their rehabilitation and recovery. The chapters are succinct, well organized, and extensively referenced. Given the lack of class I data supporting surgical treatment of supratentorial ICH most of the proposed interventions focus on the medical treatment of ICH. Among the topics discussed, management of patients on anticoagulation and critical care challenges including blood pressure control, seizures, and thromboprophylaxis are methodically reviewed and provide the latest evidence based recommendations for treatment. Dr Qureshi's expertise as principal investigator on some of the leading trials for blood pressure control is evident throughout and recommendations on clinical trial design for ICH therapies are provided in the last chapter.

The chapter on surgical treatment of ICH reviews the results of conventional craniotomy for clot evacuation reported in the STICH trials,[1,2] the results of the MISTIE II study,[3] and mentions minimally invasive options currently undergoing testing in multicenter randomized trials. The results of MISTIE III were presented and published after the release of the book and therefore not included.[4] While the primary outcome measure on the MISTIE III trial of modified Rankin Scale at 1 yr did not reach the expected threshold for significance, the per protocol analysis did show significantly greater likelihood of improved outcomes if the patients reached the end-of-treatment volume goal of <15cc, which unfortunately was reached in less than 60% of patients. These findings suggest that minimally invasive techniques capable of achieving greater clot reduction could potentially result in improved outcomes.

In summary, *Intracerebral Hemorrhage Therapeutics* presents a well-constructed compendium of the latest evidence-based recommendations for evaluation and treatment of patients with ICH. For a neurosurgical audience the book represents an excellent resource with practical recommendations and critical commentary on the results of the latest clinical trials comprising the spectrum of the disease. The surgical aspects of ICH care are not the focus of the book but are well reviewed in the context of the limited evidence available to support its use in supratentorial ICH.

Disclosures

Dr Pradilla is principal investigator for the ENRICH clinical trial sponsored by NICO corporation.

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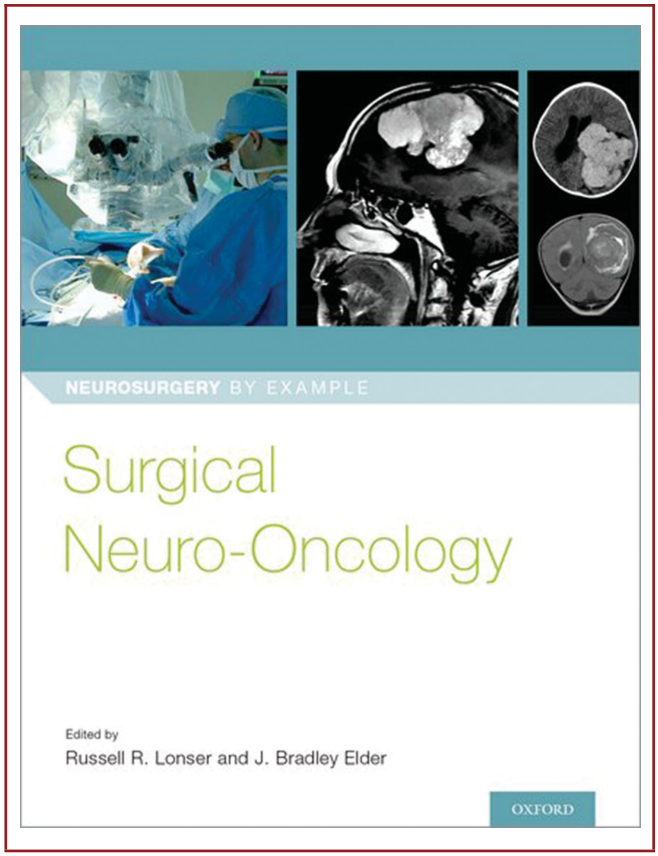
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Book Review: *Surgical Neuro-Oncology*

By: Russell R. Lonser, J. Bradley Elder, editors
Published by: Oxford University Press,
New York, New York, 2018
Softcover: 590 pp.
Price: $99.95
ISBN: 9780190696696



Surgical Neuro-Oncology, edited by Drs Russell Lonser and J. Bradley Elder, represents an important and highly pragmatic contribution to the landscape of resources on central nervous system tumor management for neurosurgeons. This book is part of a growing series edited by Dr Nathaniel Selden called "Neurosurgery by Example: Key Cases and Fundamental Principles". The collective expertise of the editors and the chapter authors in this area is a major strength of this compendium; indeed, each chapter is written by an internationally recognized surgeon. At 288 pages, this book is highly readable (and affordable) as a comprehensive resource or as a topical reference. As the series title suggests, this book is designed as a high-yield resource with immediately practical information.

Surgical Neuro-Oncology is comprised of 29 chapters that cover most of the neoplastic processes encountered by neurosurgeons in practice, from benign to malignant brain tumors, skull base pathologies, and spine oncology. Each chapter follows an identical organization: Case Presentation, Assessment and Planning, Decision-making, Surgical Procedure, Aftercare, Complications and Management, and Evidence and Outcomes. Throughout case descriptions, inset boxes address topical questions, "pearls" on important points related to diagnosis, management, complications germane to the neurosurgery oral boards structure, and "pivot points". In addition, each chapter provides a focused reference list for further reading.

The potential audience for this book is broad. The case-based structure of each chapter and extensive coverage of areas addressed in oral boards examinations offers a comprehensive resource for the junior neurosurgeon preparing for either the general or tumor-specific examination. However, the practical nature of each chapter and importance of all of the topics covered lends itself to other groups as well: the advanced medical student, residents filling out their education or particularly interested in central nervous system (CNS) oncology, and practicing neurosurgeons who wish to update their fund of knowledge in these areas. Ultimately, the conceptual framework attributed to the oral boards examination—ie, diagnosis, management, complications—is helpful regardless of its relevance to testing and therefore significantly adds to this book's utility.

As our field continues to evolve, future editions of this book will surely address some additional areas relevant to current neurosurgical care and practice. First, there should be a major focus on molecular diagnostics, especially in brain tumors. Sections on glioblastoma and low grade gliomas would benefit from a discussion of how key biomarkers—such as the IDH1 gene mutation, the TERT promoter mutation, and the 1p/19q co-deletion—are changing the way we think about diagnostics, natural history, and prognosis. In addition, a section on pediatric malignant gliomas would be helpful, particularly as we come to understand how important mutation-based diagnostics are in these pathologies. Second, there is some variation in the degree of technical detail used to describe surgical management across chapters. Optimally, chapters could have focused diagrams of positioning and incision for each case that is presented. Third, each chapter should include the most contemporary information regarding CNS pathology. For instance, it is notable that the section on hemangiopericytomas does not discuss the revision in classification of these entities in 2016 to "solitary fibrous tumor/hemangiopericytoma" along with its attendant molecular diagnostics including the NAB2/STAT6 fusions. Fourth, the book would benefit from a chapter dedicated to recurrent

glioblastoma, where newer treatments such as laser ablation could be introduced as well as other heuristics for thinking about this very challenging clinical setting. Finally, there might be an opportunity to include focused sections covering particularly complex clinical scenarios in CNS oncology, including tumors of the insula and thalamus as well as brain metastases refractory to standard management options.

Surgical Neuro-Oncology is an important contribution to the management of CNS tumors. Although it is clear that many of the entities reviewed in the book require multidisciplinary care and may not be entirely surgical in their management, its specific focus on the neurosurgeon's role in the contemporary care of these pathologies is ultimately what makes this book unique and a highly recommended addition to the libraries of current and aspiring neurosurgeons committed to taking care of patients with these often difficult problems.

Disclosures

Dr Dunn is a co-founder of Immunovalent Therapeutics. The other author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz249

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Letter: Congress of Neurological Surgeons Female International Think Tank Report: Much Progress, Still Work to Be Done

To the Editor:

Women neurosurgeons around the world have made significant advances over the last decades, but recent data confirm that a great deal of work is still needed. Benchmarks, such as the number of women graduating from neurosurgery residency programs and the number of board-certified women neurosurgeons, have markedly increased (Figures 1 and 2).[1-3] However, these numbers remain disproportionate compared to those of men in the field (Figure 3).[1-3] Analysis of this topic reveals that for all working women, parity remains elusive.[1-4] Gathering precise data on the challenges faced by women, specifically in neurosurgery, is therefore essential. Toward this aim, the Congress of Neurological Surgeons (CNS) hosted the first International Female Neurosurgical Think Tank at the 2018 annual meeting in Houston. The results of this meeting are presented.

Fourteen women neurosurgeons from around the world (Table) were joined by 2 male colleagues and 3 non-neurosurgeon female professionals. The purpose of the meeting was to reflect on:

- The current standing of international women neurosurgeons
- The ideal status of international women neurosurgeons
- Strategies to bridge identified gaps

SWOT (Strengths, Weaknesses, Opportunities, and Threats) analyses suggest that the appropriate emphasis on organizational change must be paired with changing individual behavior. Thus, a SWOT format was used to guide discussion. The results of a pre-meeting survey also served as a foundation for dialogue, shedding more insight into the professional gender gap that still exists (Figures 4–7).

"STRENGTHS" IDENTIFIED BY WOMEN NEUROSURGEONS

Beginning a discussion of perceived gender-based strengths and weaknesses creates a sense of unease, given the question of these being biological, cultural or a combination. The data suggest that social and/or communicative differences between genders do exist,[4-6] although these characteristics are likely conditioned.[6,7] Additionally, many personal qualities are observed across genders. Even the terms "strengths" and "weaknesses" are open to interpretation. One behavioral trait might be considered positive in a given environment, profession, or context, while that same quality might be viewed less favorably under different circumstances. For instance, surgeons regardless of gender manifest personality traits serving them within the hospital setting but may be negatively viewed outside of work.[5] Accepting such pitfalls, participants listed "strengths" traditionally identified as "female behavior" that served them well professionally and benefited their patients. The most common responses were as follows:

- Empathy
- Communication skills
- Willingness to collaborate
- Diversity of perspective

It should be noted that the intent of this exercise was not to perpetuate gender-based stereotypes, which can undermine gender equality and promote discriminatory views.[7] Instead, the purpose was to acknowledge that learned differences in behavior between men and women may impact self-perception, which in turn can affect one's own actions. This is corroborated by studies examining personality differences between genders and their effects on the delivery of healthcare.[4,8,9]

In addition to the above "strengths," participants discussed other "advantages" to being women neurosurgeons. First, women patients may feel more comfortable with surgeons who are also women. Numerous studies evaluating patient satisfaction substantiate that women patients often prefer same-sex physicians.[2,8-11] Second, training and practicing in a clearly disadvantageous male-dominated environment, likely generates strength and resilience as a result of overcoming these obstacles. Most women queried have, on many occasions, literally been the only female at the table, so the women felt they offered a distinct perspective from their male peers. This contributes to a diversity of thought that can be valuable clinically and academically.

"WEAKNESSES" IDENTIFIED BY WOMEN NEUROSURGEONS

Three significant vulnerabilities were overwhelmingly identified by the women as negative "female" behavior:

- Insecurity
- Impostor syndrome
- Professional altruism (one's hard work and efforts being handed or credited to another)

Every member of the group recalled instances where they questioned themselves or felt inadequate, even when knowing this not to be true. These feelings of self-doubt are not unique to the women participants questioned. In analyzing gender differences among students of science, technology, engineering, and mathematics (STEM), females are consistently found to exhibit more anxiety and negative self-worth than males, even when outperforming them,[12,13] perhaps contributing to the higher attrition rates of female STEM students.[12,14] Likewise, women medical students have been found to devalue their performances on clinical rotations,[4,10] potentially deterring them from pursuing

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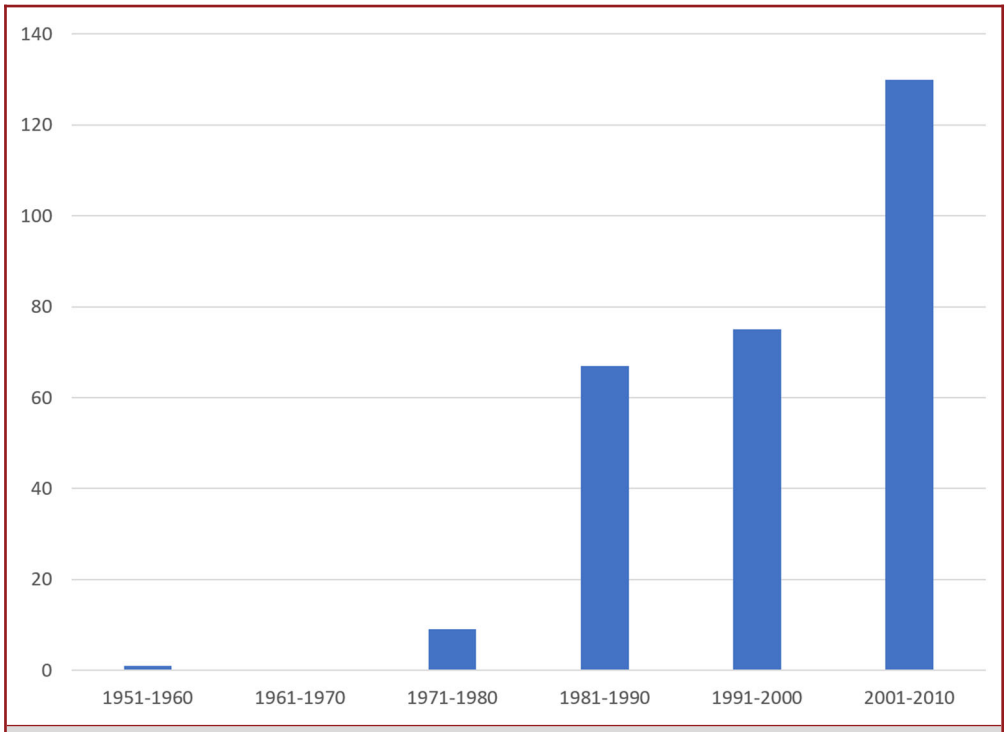


FIGURE 1. *Number of women graduating from US neurosurgery residency programs from 1951 to 2010 (data points accrued from Benzil et al, Appendix 2[1]).*

competitive surgical specialties.[15] European data evaluating the impact of neurosurgical training on career planning and anxiety between genders also support this phenomenon.[16] In a survey of European neurosurgeons completing their training, women tended to feel less confident to work on their own and were twice as likely as men to experience anxiety about their future careers.[16]

The men participating were quick to acknowledge that they also suffered from insecurities, particularly the impostor syndrome. This suggests that perhaps the impostor syndrome differs in some important way for men and women neurosurgeons. Some possibilities regarding the syndrome include the following:

- Incidence
- General impact
- Specific impact on career choices (including withdrawal from the specialty)

Studies have shown that gender highly influences how individuals react to criticism, challenges, and mistakes.[1,4,12,15,17] This could shape the effects of the impostor syndrome. Together, such factors contribute to and influence a woman's reaction to such self-doubt, resulting in the higher rates of attrition seen in women across all surgical specialties, particularly neurosurgery.[18]

The lack of role models and mentors for women may further aggravate this condition, particularly if the learning style of women differs from that of men, as data suggest.[1,4,12,18] Undoubtedly, women neurosurgeons suffer a paucity of mentors of any gender perpetuating the cycle of self-deprecation.[1,2,4,18,19] Limitations of support for women are likely compounded by a tendency of women to see successes as a team effort and to allow others to take credit for their ideas and accomplishments. Participants became animated in relating multiple episodes when a woman's ideas were usurped by a man who was a colleague. Both behaviors serve to veil the successes of women from their peers, superiors, and sometimes even from themselves.

THREATS IDENTIFIED BY WOMEN NEUROSURGEONS

The threats identified by the women neurosurgeons were remarkably universal for women across all professions. These threats were as follows:

- Fewer opportunities for promotion and leadership
- Unequal pay for equal work
- Overcoming prejudices against women by patients and peers
- Limited role-models and mentors
- Navigating work-life challenges, particularly during pregnancy and when raising small children

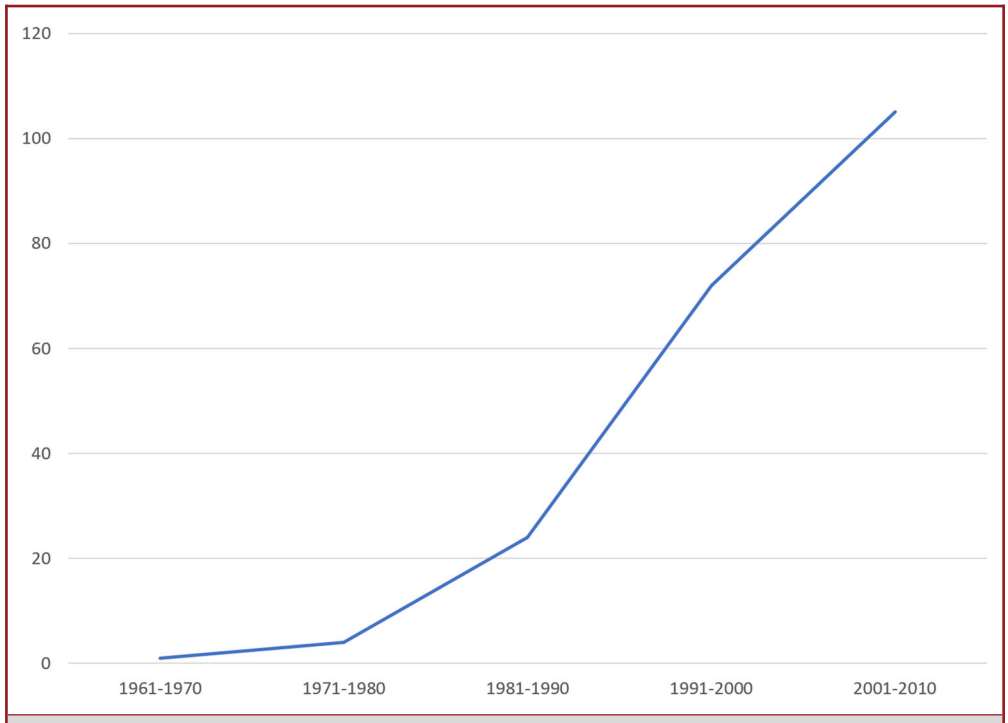


FIGURE 2. *Number of ABNS board-certified women neurosurgeons from 1961 to 2010 (data points from Renfrow et al[2]).*

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A common refrain in the meeting was that women felt they had to work and study harder, complete more fellowships, and/or receive more degrees just to be recognized as an equal to their men counterparts. These concerns have been frequently reported in other studies evaluating women in a male-dominated environment.[1,2,4,10,15,18-20] This is perhaps due to awareness that promotions for women are slower and rates of attrition are higher, despite more women pursuing careers in STEM and medicine.[1,2,14,16,18,20,21]

However, even with increased efforts by women to strengthen their credibility, women authorship in scientific journals around the world remains notably lower than that of men.[4,20] This disparity is even greater in higher impact journals.[20] Such trends are similarly seen with NIH funding for women investigators.[7,9] Intensifying these barriers, European data indicate that women start their careers with fewer research-related resources than men in academic medical careers, thus setting up women for decreased scientific productivity.[16] Gender disparities also extend to salary differences between working men and women, in both medical and nonmedical professions.[1,4,19] Promotional opportunities are also affected. There are only 4 neurosurgical programs in the US, as of recently, with women serving as Neurosurgery Chairs, yet this is still too few.

Outside the US, some women neurosurgical participants stated that while there is little or no public pay discrepancy across genders in their country, implicit patient bias (choosing men surgeons more frequently) does play a role. This indirectly impacts income and promotion, and is also a well-described phenomenon.[10,14,22] Women discussants from all countries felt that male colleagues also unwittingly displayed unconscious bias. These sentiments are corroborated by evidence suggesting that men may be more actively sought for collaborative endeavors by their peers, maintaining a "boys' club" environment that promotes the professional advancement of men.[4,15] Interestingly, several women described that their experience of discrimination by their peers changed when they became mothers. As a result of this milestone, they began to be held to different standards, another frequently reported experience.[4,23,24]

It was enlightening to learn that in some countries, the neurosurgery match is blind to gender, which dramatically reduces unconscious bias. In these systems, candidates' scores in prioritized categories are available for program review rather than individual applications. Based on recent data, this approach will more likely support meritocracy for the residency match, as applicant gender may negatively impact neurosurgical matching for women.[25] Despite such innovative strategies, universally, there are still not enough neurosurgeons of either sex who are willing to mentor women, and far too few women in the field to change the unconscious biases of neurosurgeons and patients.[1,4,10,12,15,19,20,23,24,26]

The challenges of work-life harmony/integration generated significant discussion. This challenge is felt for women across the training and practice spectrum, experienced even in high school and college.[10] It also extends across countries to varying

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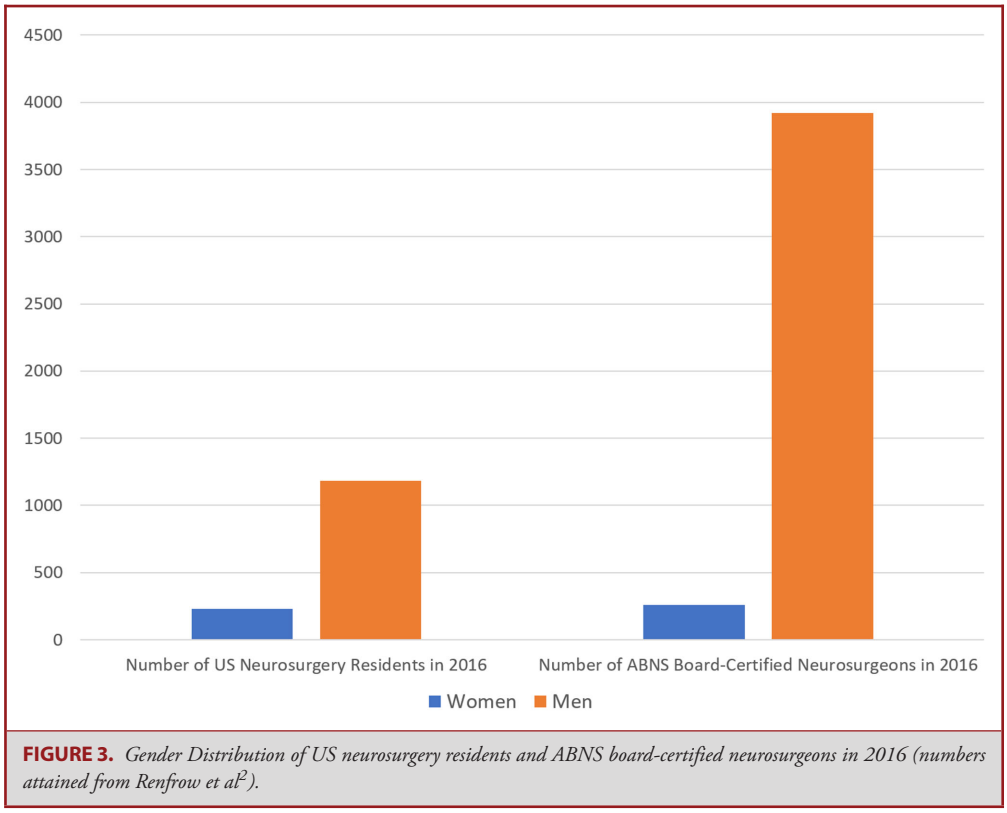


FIGURE 3. *Gender Distribution of US neurosurgery residents and ABNS board-certified neurosurgeons in 2016 (numbers attained from Renfrow et al[2]).*

TABLE. Countries Represented at CNS International Female Neurosurgical Think Tank

	Total female neurosurgeons	Department chairs
US	9	1
Brazil	1	0
Netherlands	1	0
Portugal	2	0
Spain	1	1

degrees, though some are more effective than others in addressing this. For example, in Portugal, all working women are offered maternity leave for up to 6 months, which may make neurosurgery more appealing to young women. Female neurosurgeons who have families during their residency training can make up this 6-months, period later, resulting in critical flexibility. Disappointingly, child care support is not readily available nor supported by any of the hospitals of the women discussants from any country.

This pervasive problem of work-life balance affects females across medical specialties and STEM disciplines,[1,4,10,14,15,18,24] with limits to child care being a key element. The differential hours, particularly for women in medicine, aggravates this issue. Moreover, women who are primary wage earners or with substantial professional demands often still serve as primary care givers at home and shoulder a disproportionate burden of home responsibilities.[23] These family circumstances greatly impact the chances of promotion and leadership for women that might otherwise happen at critical stages of their careers. Better systems to protect free time and family life, for both men and women neurosurgeons, will benefit all.

Ultimately, such gender imbalance leads to poor self-esteem, reduced resilience, and less career satisfaction for women.[1,4,10,15,18,24] This may, in part, explain why the board certification rates for women in neurosurgery remain lower than for men in the US and Europe.[1,2,16,19] While there may never be an equal representation of women in the workforce,[24] without the presence and visibility of more women achieving success as neurosurgeons, such as promotion and leadership, it will remain exceedingly difficult to overcome the discriminations of colleagues and patients described above.

OPPORTUNITIES IDENTIFIED BY WOMEN NEUROSURGEONS

Despite extensive discussion surrounding the challenges faced by women in neurosurgery, participants remained hopeful and excited when the conversation shifted into opportunities for

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Q1 As a woman in Neurosurgery, what is the biggest challenge you have faced in your career/practice?

Common Themes:

General Theme	# Responses
Discrimination/bias/prejudice against female surgeons	3
Unequal pay/Lack of Promotion or Leadership Access	4
Work-life Balance/Family related challenges	4

Q2 What is one thing that may have helped you, or could help you in the future, to address and overcome this challenge?

Common Themes:

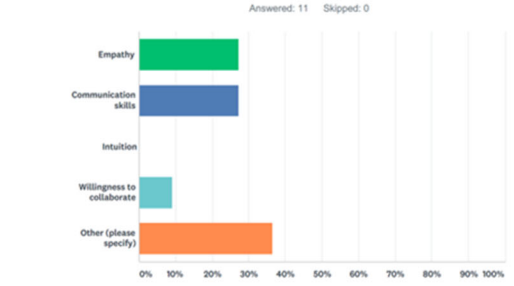
General Theme	# Responses
Better mentors and role models	4
Specific training or education (leadership, economics, etc)	3
Improved policies, systems and support from colleagues/society	3

Q1 & Q2 Complete Responses – Side by Side

To overcome prejudice against female surgeon by both patients and peers.	To have female neurosurgeon mentorship. This issue is not even realized by the most apparently comprehensive male neurosurgeon.
Implicit bias	Women surgeons who are not pathologic
Discrimination	Systems policies with teeth
Unequal pay	Better knowledge of trends and economics of these issues
Promotion	Leadership training
Promotion	Learning how to self-promote, learning how to ask for things from leadership
Having formal and informal connection the leadership	Having a buddy - what I mean with this opportunities arise and committee slots need to be field - most of the time people in leadership position name peers they know of or have spend time with - men have a much better network then women
Balancing research, clinical work and family	Better role models who aren't workaholics!
Work-life balance	Social and educational advances
I always felt that I had to work and study three times more to be recognized. That's why now I have my PhD and 2 fellowships. I've faced some difficulties, but with hard work, I've obtained the recognition of my team and coworkers.	Hard work.
Biggest challenge was performing surgeries during pregnancy, especially during my third trimester.	support from fellow neurosurgeons

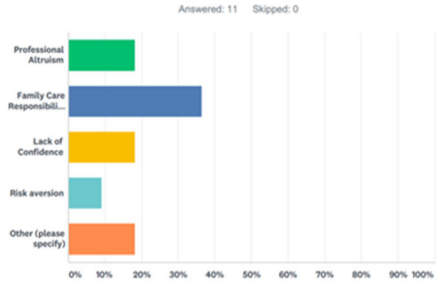
FIGURE 4. *Questions 1 and 2 (Q1, Q2) from pre-meeting survey.*

Q3 What unique strengths do women bring to the field of Neurosurgery?



ANSWER CHOICES	RESPONSES	
Empathy	27.27%	3
Communication skills	27.27%	3
Intuition	0.00%	0
Willingness to collaborate	9.09%	1
Other (please specify)	36.36%	4
TOTAL		11

Q4 What unique weaknesses (real or perceived) impact women's ability to be successful in neurosurgery?



ANSWER CHOICES	RESPONSES	
Professional Altruism	18.18%	2
Family Care Responsibilities	36.36%	4
Lack of Confidence	18.18%	2
Risk aversion	9.09%	1
Other (please specify)	18.18%	2
TOTAL		11

Q3 Other Responses:

Team players, self-awareness,
Diligence technical skills
all of the above, also different ideas about how to address problems
All of the above - probably empathy and collaboration at the top

Q4 Other Responses:

Imposter syndrome
None-women would be as if not more successful if on even playing field

FIGURE 5. *Questions 3 and 4 (Q3, Q4) from pre-meeting survey.*

improvement. Agreed upon strategic efforts for the group moving forward included:

- Recruiting more women into neurosurgery
- Promoting mentorship for women
- Developing women leadership opportunities
- Engaging women in neurosurgery globally
- Supporting women

Among the many initiatives resulting from the CNS International Female Think Tank will be efforts to recruit more women into the field. Young girls and women will be targeted in a "This Is Neurosurgery" social media campaign to build awareness and to showcase the many faces of women neurosurgeons around the world. There are substantial data demonstrating that an absence of role models for women plays a role in the self-doubt of women in pursuit of medical and STEM

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Q5 What trends or conditions may make it easier or harder for women to pursue a Neurosurgical career over the next 5-10 years?

Common Themes:

General Theme	# Responses
Increasing number of women in neurosurgery, Greater visibility for women surgeons	5
Changing culture - Work-life balance emphasis, social role changes, shift toward dual career couples	6

Complete Responses:

The presence of more and more women in the field would make it easier for more women to embrace Neurosurgery.
Better women mentors
Greater number of women present
numbers are increasing, childcare is better, increased awareness
Encouragement in conferences and social media (or WhatsApp groups). This is pretty strong in Brazil.
More emphasis on avoiding burnout and on work life balance makes it easier
Family care responsibilities, real or perceived. The sometimes hostile environment which appears to be improving overall.
now and in the near future more and more MALE neurosurgeon won't be fully supported workers anymore (aka having a spouse at home) as dual career couple become more common the 24-7 culture in neurosurgery will change
Desire for less rigorous training to start family
Easier: technology, social and educational role advances
maternal responsibilities may make my neurosurgical career harder.

Q6 In what country do you currently practice?

Brazil	1
Philippines	1
Portugal	1
Spain	1
USA	7

No trends or themes were identified by location (US vs OUS)

FIGURE 6. *Questions 5 and 6 (Q5, Q6) from pre-meeting survey.*

specialties, discouraging them away from such professions, while also fostering further bias in both genders.[1,4,10,12,15,19,21-24] Thus, this campaign may help break down preconceptions, while allowing young girls and women to imagine themselves as neurosurgeons too. Reaching girls as early as elementary or high school would effectively increase the number of females who pursue careers in neurosurgery and other traditionally male-dominated careers. Additionally, as a result of the meeting, several efforts are underway to better connect women in neurosurgery internationally utilizing social media. Networking events will be held to help women find professional resources, connections, and friendships that may result in opportunities not otherwise possible. These efforts are intended to help establish a critical mass of female neurosurgeons, potentially further encouraging more women to pursue the field.

Mentorship for women was also felt to be paramount in overcoming bias and discrimination and was another agenda item resulting from the meeting. Mentorship is needed for women who are considering a career in neurosurgery, as well as for those in residency susceptible to attrition and those who are faculty striving for professional advancement. Men and women must both serve as mentors for women neurosurgeons, and both genders should be encouraged to fulfill this role. This unmet need for the mentorship of women is ubiquitous.[1,2,10,15,19,26] Any concerns raised by men mentoring women as a result of the #MeToo type issues should be easily dealt with through systemic organization of appropriate mentoring and coaching programs. Over the years, Women in Neurosurgery (WINS) in the US successfully established several mentorship efforts for women. WINS has also recently collaborated with the CNS and the American Association of Neurological Surgeons to further promote these programs at each society's annual meeting. Online resources, such as webinars, are available through the CNS and through the Joint Section of Women in Neurosurgery (http://www.neurosurgerywins.org), as are awards and other opportunities for women globally to apply throughout the year. The CNS International Female Summit aims to partner with WINS in the US and with women in other countries to strengthen these mentoring efforts and to make them accessible to young girls and women worldwide.

It is also imperative that women pursue leadership courses and education to become more effective at promoting themselves and leading others. Only when women hold seats as leaders, next to men who are regarded as leaders, can prejudices truly be overcome. As such, attendees from the CNS Female International Think Tank have pledged to work with the CNS to develop a leadership course and curriculum geared towards women neurosurgeons. Another mechanism that can foster the promotion and leadership of women is the establishment of WINS sections within organized neurosurgical societies in countries around the world. Although some countries, such as Brazil, already have a formal WINS organization, many other countries do not. Launching such associations would generate more opportunities for women to hold positions of leadership and to have their

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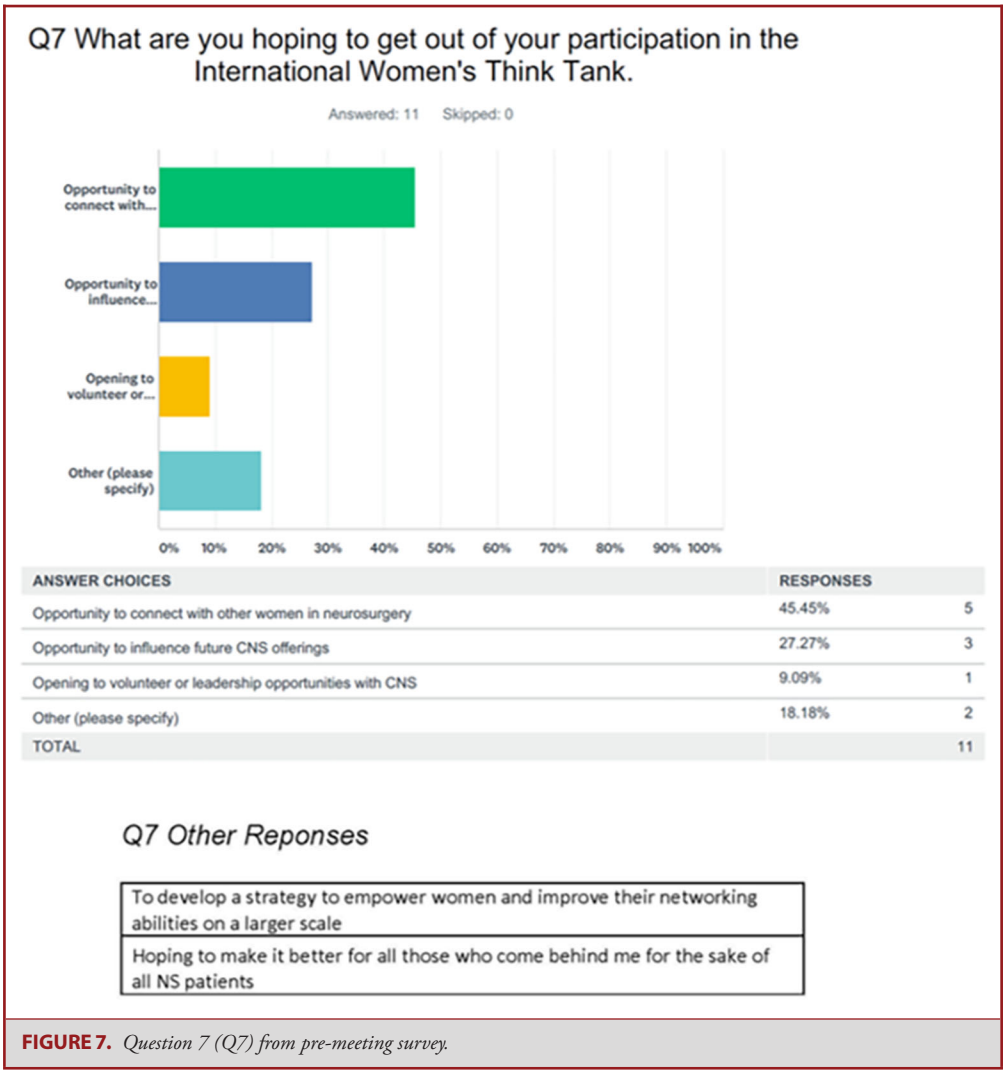


FIGURE 7. *Question 7 (Q7) from pre-meeting survey.*

voices heard amongst their men colleagues. WINS is also vital in protecting, supporting, and advancing women in the field, irrespective of the number of women neurosurgeons in the region. Thus, helping to create WINS globally is likewise an objective arising from the meeting.

Finally, it is vital to eliminate barriers for women in neurosurgery. Transparency and equity in pay across genders is a key component of this equation, as this reaffirms the worth of female neurosurgeons and would represent a tangible first step in equality of labor.[2,16,19] Similarly, developing a mechanism across organized neurosurgery in all countries to allow women to report true harassment and sexual discrimination without backlash and with an appropriate response. This would help to ensure the protection of women throughout their careers.[1,4] Lastly, devising approaches that support women who have families, such that they can simultaneously be successful neurosurgeons, are also needed. Hence, institutions and training programs should find creative solutions to allow a work-life integration, which would likely improve the quality of life for both men and women in the field.

REFLECTIONS

The 30th anniversary of WINS will be celebrated in 2020, representing an impressive milestone to reach. It also offers a chance to reflect on the progress achieved by women in neurosurgery around the world. Yet, still, much work remains. Open conversations and thoughtful strategies for gender equality are essential for the betterment of the field. These efforts require the help of both men and women to generate meaningful change for the future of neurosurgery.

Disclosures

This publication was made possible by the Clinical and Translational Science Collaborative of Cleveland, KL2TR002547 from the National Center for

Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Dr Sweet receives grant support from the National Institutes of Health (2KL2TR000440) and serves on the scientific advisory board of Koh Young Inc. Dr Sweet also serves on the Congress of Neurological Surgeons Executive Committee and is on the Neurosurgery Editorial Board. Dr Rao is the President of the Congress of Neurological Surgeons Executive Committee and is on the Neurosurgery Editorial Board. Dr Kalkanis is the President Elect of the Congress of Neurological Surgeons Executive Committee and is on the Neurosurgery Editorial Board. Dr Sharan is the Past President of the Congress of Neurological Surgeons Executive Committee and is on the Neurosurgery Editorial Board. Dr Benzil is a partner in Benzil Zusman LLC and serves on an expert panel for BrainLab. The Congress of Neurological Surgeons Female International Neurosurgical Think Tank event was sponsored by Stryker, but they had no role in its content.

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Acknowledgments

The Congress of Neurological Surgeons (CNS) would like to acknowledge and thank the participants of this meeting: Ellen Air, MD, PhD; Nadia Atai, MD, PhD; Sharona Ben-Haim, MD; Lola Chambless, MD; Ana Luís, MD; Karin Muraszko, MD; Maryam Rahman, MD; Carla Reizinho, MD; Martina Stippler, MD; Sarah Woodrow, MD; Idoya Zazpe, MD, PhD. These efforts were supported by the CNS Staff: Michele Hilgart, Courtney Johnson, and Regina Shupak.

10.1093/neuros/nyz254

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06/22/2023

Letter: When Less is More: Dexamethasone Dosing for Brain Tumors

To the Editor:

We are writing to highlight the discrepancy in dosing schedules for corticosteroids used to treat peritumoral edema between the neurosurgical community and the neuro-oncology community and suggest that it may be time to re-evaluate the dosing of dexamethasone for brain tumors.

Corticosteroids have been ubiquitously used to treat brain tumor patients with cerebral edema since the 1950s. In particular, dexamethasone, due to its low mineralocorticoid potency and high glucocorticoid activity, is arguably the most commonly used symptomatic agent out of the limited armamentarium available to physicians caring for brain tumor patients. This widespread practice traces its origin in part to the landmark paper by Dr Joseph Galicich and colleagues from the University of Minnesota in 1961.[1] In this study, 14 patients with brain tumor-related cerebral edema were treated with an initial bolus of 10 to 40 mg of dexamethasone, followed by a regimen of 4 mg intramuscularly every 6 h. A total of 13 out of the 14 patients experienced a significant improvement in their neurological symptoms, and dexamethasone was hence deemed a "safe and highly effective" agent in the treatment of tumor-related cerebral edema. Since that time, it has been standard practice for dexamethasone to be administered to patients every 6 h, including, frequently, in the middle of the night.

While the benefit of dexamethasone can be dramatic both clinically and radiographically, particularly in patients with brain metastases and lymphoma, balancing the side effects remains a real challenge, and overuse of dexamethasone is common. Steroid-related toxicities present a significant concern over time and include iatrogenic Cushing's syndrome, behavioral issues, myopathy, opportunistic infections, and osteoporosis. In addition, early steroid use in primary brain tumor patients has been associated with increased morbidity and mortality.[2] As newer therapies attempt to augment the immune response in the treatment of brain tumors, the use of steroids for symptomatic relief has become counterproductive in many cases. Every attempt should be made to start at the lowest effective dose and taper as rapidly and as safely as possible.

Dosage and tapering of dexamethasone in brain tumor-related cerebral edema are physician, specialty, institution, and patient dependent. Over time, there has been a growing discrepancy between the dose and schedule of dexamethasone used by the neurosurgical and the neuro-oncology communities. Most neurosurgeons initiate dexamethasone at 4 mg every 6 h, following a bolus, and maintain an every 6 h schedule for lower doses. In contrast, most neuro-oncologists administer dexamethasone twice daily or even once daily. These schedules are significantly easier for patients and have not been associated with diminished efficacy.

Dexamethasone has a biological half-life of 36 to 54 h (despite a plasma half-life of about 4 hs) and can provide a symptomatic benefit for a prolonged duration.[3] A study published in 1990, which utilized autoradiography to monitor capillary permeability to study peritumoral edema in a C6 rat glioma model, revealed that a single dose of dexamethasone maintained a reduction in capillary permeability over a 12-h course.[4] Another study corroborated a substantial reduction in vascular permeability and water content of tumor and peritumoral brain tissue in RG2 rat glioma following twice daily dexamethasone dosing.[5] Although rigorous patient studies on twice per day dexamethasone dosing are lacking, a small pilot study of 14 patients with intracranial metastases on a twice daily tapering regimen starting at 8 mg twice a day showed similar rates of clinical response and no neurological decline when compared to historical cohorts.[6]

Administering corticosteroids every 6 h frequently can result in poor sleep due to medication-related effects or medication administration itself, contributing to increased daytime fatigue. In a population where preserving the quality of life is paramount, and in the absence of evidence to justify more frequent dosing, we hope the neurosurgical community will join the neuro-oncology community and consider changing its practice to once or twice a day dosing of dexamethasone for brain tumor patients.

Disclosures

Dr Colman is on the Advisory Board for and is a consultant for Abbvie, Foundation Medicine, Innocrin, Tactical Therapeutics, Deciphera, Newlink Genetics, Best Doctors, Merck, and Karyopharm Therapeutics, and receives research funding (Site PI/Institutional Contract): Newlink Genetics, Plexxikon, Kadmon, Orbus, Merck, DNATrix, Abbvie, Beigene, and Forma. Dr Lo is on the Advisory Board for Gilead Sciences and is a consultant for Viiv Healthcare. Dr Mellinghoff receives research funding from General Electric, Amgen, and Lilly, has advisory roles with Agios, Puma Biotechnology, and Debiopharm Group, and has received honoraria from Roche for a presentation. Dr Mehta is a consultant for Varian, Abbvie, Celgene, Astra-Zeneca, Tocagen, and Blue Earth Diagnostics, and is on the Board of Directors for Oncoceutics. Dr Lassman has received honoraria/travel/research support (prior 12 mo, all outside the submitted work) from Karyopharm, NW Bio, Agios, AbbVie, Sapience, Oncoceutics, Novocure, Tocagen, Genentech/Roche, Amgen, Millenium, Celldex, Novartis, Pfizer, Aeterna Zentaris, Pfizer, Kadmon, VBI Vaccines, Beigene, and Bioclinica. Dr Ahluwalia has received grants/research support from Astrazeneca, Abbvie, BMS, Bayer, Incyte, Pharmacyclics, Novocure, and Merck, has received honoraria or consultation fees from Elsevier, Wiley, Astrazeneca, Abvvie, VBI Vaccines, Flatiron, Varian Medical Systems, and Prime Education, and is a stock shareholder in Doctible and Mimiva.

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10.1093/neuros/nyz186

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Letter: Older Patients Have Better Pain Outcomes Following Microvascular Decompression for Trigeminal Neuralgia

To the Editor:

We have read with a great interest the invaluable research by Bick et al[1] that has been published in the latest issue of *Neurosurgery*. In this retrospective review of 135 patients with typical trigeminal neuralgia (TN) with radiological evidence of neurovascular compression (arterial and/or venous), the authors demonstrated that patients older than 60 yr have better pain outcomes compared to younger patients through univariate and multivariate regression analysis. The article is invaluable as the literature is still scarce on the subject and the role of various risk factors on determination of outcome of those with TN is a matter of debate.

The outcome of TN as indicated by the authors is affected by several confounders that make it hard to determine the exact role of factors. The authors have indicated that they have ran a literature review to determine the current confirmed factors affecting the outcome in their analysis. In the current study, disease duration, having undergone pervious procedures for TN, the presence of arterial compression, preoperative trigger points, preoperative medication responsiveness, and dermatomes involved, were included as the factors affecting the outcome.[1] When looking at the literature there are several more important variables available that could or should have been included in the analysis in order to decrease the role of confounders and bias in the results of the study. The major risk factor for TN is multiple sclerosis (for unilateral TN—risk ratio [RR], 20.0; 95% CI, 4.1-59.0).[2] Hypertension is a risk factor in women (RR, 2.1; 95% CI, 1.2-3.4), but the evidence is less clear for men (RR, 1.53; 95% CI, 0.30-4.50).[2] A history of TN in a first-degree relative is also a minor risk factor.[3] Recent lines of evidence have also demonstrated that diabetes mellitus (DM) is considered a risk factor for development[4] and poor outcome[5] of patients with TN undergoing microvascular decompression. The role of obesity and other comorbidities[5] and also the presence of other psychiatric disease such as depression have also been investigated vastly with various results and conclusions.[6] Although none of these previous studies are flawless, and the results are considered as level III of evidence; including them in a multivariate regression model of similar studies is recommended to decrease the role of confounders.

The other issue worth consideration is determining the cut-off value for age in these patients. How did the authors come to 60 yr as the cut-off value for the age? This value could be estimated both clinically or based on ROC analysis models. However, there is no description of its calculation in the article. In addition, the comparisons have all been made based on a categorical age (above and below 60 yr). They could also consider the age as a parametric variable and calculate the Pearson correlation coefficient regarding the pain outcomes. The age could have also been compared between those with favorable and unfavorable pain outcomes as a parametric continuous variable using the appropriate tests. As addressed in the current issue of the journal, the concept of the biostatistics should be used to better analyze and understand the complex association of clinical variables in order to come to an appropriate clinical conclusion, which will benefit the patients.[7]

Again, we thank the authors for their novel idea and nicely designed and presented study that shed light on some aspects of the TN outcome factors; however, we believe when coming to a robust conclusion such as the one presented by this study, we should be cautious, as their might be several other factors that would affect the results.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We would also like to acknowledge the editorial assistance of Diba Negar Research Institute for improving the style and English of the manuscript.

10.1093/neuros/nyz195

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In Reply: Older Patients Have Better Pain Outcomes Following Microvascular Decompression for Trigeminal Neuralgia

To the Editor:

We appreciate the thoughtful commentary by the authors[1] on our article.[2] In our paper, we reviewed the outcomes of patients with typical (type I) trigeminal neuralgia (TN) who underwent microvascular decompression (MVD) at our center between 1/1/2004 and 12/31/2013. We divided patients into 2 age groups, less than and greater than 60 yr of age, for analysis and performed univariate and multivariate analysis to determine the effect of age on outcome following MVD for TN. Variables investigated for relationship to outcome following MVD and included in univariate and/or multivariate analysis were age, gender, TN laterality, preoperative disease duration, history of previous procedures for TN, intraoperative finding of arterial compression, presence of preoperative trigger points, preoperative medication responsiveness, and dermatomes affected by TN. The authors note that several other variables have been identified in the literature as potentially associated with TN that we did not include in our study, namely multiple sclerosis, hypertension, history of TN in first degree relative, and comorbidities including diabetes mellitus, obesity, and depression.

A multitude of variables have been variably associated with incidence of TN and outcomes following MVD for TN. With our limited sample size and study power we attempted to identify the most relevant variables to control for in multivariate analysis and therefore searched for factors previously associated with TN, however, we agree with the authors that it would be interesting and important to investigate the role of factors associated with TN incidence in outcome following MVD in future larger studies. Multiple sclerosis-associated TN often has an atypical component and is thought to be caused by myelination changes rather than neurovascular compression.[3] Inclusion criteria for our study included presence of typical TN and radiographic neurovascular compression, as such none of the patients included in our study had multiple sclerosis. While as the authors note one study found that hypertension was associated with TN in women,[4] we did not find evidence of an association between hypertension and outcome following MVD for TN in the literature.[5,6] The authors note that family history of TN is associated with increased risk for TN. While we also did not find evidence of family history of TN being associated with outcome following MVD in the literature, this association would be interesting to investigate in the future. The previously reported association between diabetes, obesity, and outcome following MVD is with a higher rate of reoperation within 30 days.[7] This study used data from a database to associate several predictive factors with complications follow MVD. As such it is not possible to determine reason for reoperation from the study data; however, it is possible that many of the reoperations were related to complications such as cerebrospinal fluid leak or infection rather than residual pain given the timeframe. We agree that data correlating these and other comorbidities with pain outcomes following MVD for TN would be interesting and useful in a larger study.

Several studies have previously investigated the effect of age on complications following MVD for TN. These studies have used age cut offs from 60 to 75 to divide patients into different age groups.[8-15] We chose an age cut off of 60 based on these previous studies and to maximize our statistical power, given the relatively lower number of elderly patients in our patient group. Further studies using age as a continuous variable would help to better elucidate the relationship between age and outcome following MVD. There are many possible factors that could help to predict pain outcomes and complications following MVD for TN. Continued study will help to better define the most important factors and aid in improved patient selection for this procedure.

Disclosures

D. Eskandar receives grant funding from the US Army Research Office and Defense Advanced Research Projects Agency and has received research funding from and served on advisory panels for Medtronic and Cyberonics. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz197

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06/22/2023

Letter: A Reliable Grading System for Prediction of Chronic Subdural Hematoma Recurrence Requiring Reoperation After Initial Burr-Hole Surgery

To the Editor:

We read with great interest the article by Stanišic et al.[1] In this prospective study, they conducted the proposed 3-component scoring system "Oslo CSDH Scale" to predict CSDH recurrence requiring reoperation (RrR), in which 3 types of strong independent predictors (hematoma density on preoperative computed tomography (CT) scans, preoperative volume, and postoperative residual cavity volume) were investigated by regression analysis. Although the study clearly characterizes the relationship between postoperative RrR, following burr-hole evacuation, and the above-mentioned predictors, several issues deserve further discussion.

The high rates of postoperative recurrence in CSDHs remain a serious concern for neurosurgeons despite various attempts have been made to understand this complex disease entity. However, the definitions of postoperative recurrence have not yet been thoroughly established. In current literature, 3 forms of recurrence definitions have been applied in clinical practice. (1) Radiological recurrence, Nakaguchi et al[2] in 2001 (recurrence: 21 lesions; reoperation: 16 lesions). Reoperation is indicated in patients (pts) with neurological deficit. (2) Radiological and symptomatic recurrence (with or without neurological deficit), Oishi et al[3] in 2001 (recurrence: 10 pts; reoperation: 9 pts). Patients who have symptoms that slowly subsided are not required for reoperation. (3) Radiological and symptomatic recurrence with neurological deficit, Stanišic et al[1,4] in 2013 and 2017 (107 pts). Patients who meet these criteria for enrollment undoubtedly require reoperation. The respective independent variables, as determined from regression analysis, aid to predict recurrence to various extents, which can range from merely deserving presurgical caution with conservative medications, eg, dexamethasone or tranexamic acid (from patient datasets of criteria 1 and 2) to invasive measures such as surgical necessity (from patient datasets of criteria 3). We believe that the importance to identify the appropriate prodromal patients who might benefit from early intervention is as important as the surgical treatment strategies.

The mechanisms underlying CSDH recurrence remains controversial. The brain may be difficult to rebound back postoperatively due to the inelasticity in atrophic brains, or excessively extended postoperative subdural space, which was occupied preoperatively by CSDHs with bilateral or skull base involvement. Delayed brain expansion postoperatively will postpone the obliteration of subdural spaces, which facilitates the brain shifting and possibly tearing of bridging veins.[5] As the authors cited, we previously quantified the extent of brain re-expansion using quantitative volumetric image analysis method. We proposed that bilateral CSDHs exhibited significantly larger residual hematoma volumes than the unilateral one postoperatively.[6] Bilaterality, being a critical characteristic associated with CSDH recurrence, ought to be considered with respect in the grading system for recurrence prediction.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz221

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06/22/2023

In Reply: A Reliable Grading System for Prediction of Chronic Subdural Hematoma Recurrence Requiring Reoperation After Initial Burr-Hole Surgery

To the Editor:

We thank the authors, Kung W-M et al,[1] for their interest in our paper.[2] We have already presented additional explanations regarding the paper.[3]

Current evidence suggests that patients with symptomatic chronic subdural hematoma (CSDH) are usually managed surgically, but both the efficacy and safety of this management have not been substantially improved over the last few decades. Despite various attempts that have been made around the world, there still remains no consensus about which surgical technique is more appropriate and what the optimal duration for postoperative drainage is for individual patients with CSDH. We agree with the authors that there is still no consensus regarding the definition of postoperative relapse of lesions. Moreover, there still remains no consensus regarding the definitions of other important outcomes after the surgical management of a lesion, such as curing the patient of the lesion, as well as the mortality caused by the lesion, the functional disabilities of the patient in performing activities of daily life and the decreases in the quality of life caused by the lesion. Furthermore, there still remains great variability in the enrolled clinical and radiological features related to CSDH in clinical research as well as uncertainties regarding postoperative continuance of antithrombotic agents in older patients with a CSDH. Thus, currently, there is a paucity of high-quality evidence to provide both, clear clinical guidance with respect to management strategies of patients with this lesion and comparisons of treatment outcomes between clinical studies.

Based on the authors' quantified data obtained at three time-point measures of CSDH in 10 operated patients with unilateral lesion and 10 operated patients with bilateral lesion,[4] the authors wrote in the Letter to the Editor that "Bilaterality, being a critical characteristic associated with CSDH recurrence, ought to be considered with respect in the grading system for recurrence prediction".[1] The authors made no effort to validate the proposed 3-component grading system for the individual prediction of CSDH recurrence requiring reoperation after initial surgery (The Oslo CSDH Scale), but, in fact, they suggest the enlargement of the grading system with an introduction to the bilaterality of lesions as a new component of the grading system.

The bilaterality of CSDH has long been discussed, without consensus, as a characteristic of the lesion contributing to a higher risk of postoperative recurrence compared with unilaterality. The reason for this high risk of recurrence has not been thoroughly characterized, but inappropriate postoperative re-expansion of the atrophic brain was considered as the main reason. However, our comprehensive analysis including volumetric data obtained at two time-point measures of CSDH in 84-operated patients with unilateral lesions and 23-operated patients with bilateral lesions showed that the bilaterality of lesions could not predict postoperative recurrence.[5] Furthermore, our analysis of these quantified data demonstrated that the preoperative and the postoperative volume of a unilateral CSDH in an individual patient may be larger than the sum of the preoperative volume and the sum of the postoperative volume of a bilateral lesion in another individual patient.[5] In another analysis of quantified data obtained at three time-point measures of CSDH in 44-operated patients with unilateral lesions and 10-operated patients with bilateral lesions, no difference was found in the postoperative recurrence rate between unilateral and bilateral cases.[6]

As we pointed out, for individual stratification of the risk for postoperative recurrence requiring reoperation, the most predictive characteristics are the appearances of the CT images which have a greater rebleeding tendency and high protein exudation rate, and large preoperative and large postoperative lesion volumes, regardless of whether the lesions were unilateral or bilateral.[2] Thus, recurrence requiring reoperation is more closely related to bleeding tendency, inflammatory exudation and brain ability to re-expand postoperatively rather than bilaterality. Thus, we do not support the authors' suggestion regarding enlargement of the grading system with the introduction of bilaterality of lesions as a new component. Further well-designed prospective large-scale population-based studies are needed to provide validation of the Oslo CSDH Scale.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz224

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06/22/2023

Letter: Congress of Neurological Surgeons Systematic Review and Evidence-Based Practice Guidelines on the Role of Surgery in the Management of Adults With Metastatic Brain Tumors

To the Editor:

We read with interest the paper by Nahed and colleagues,[1] who have reviewed and summarized the literature data about the role of surgery and radiotherapy in the management of adult with metastatic brain tumors (BMs). Considering the complex of this topic and the relevance to daily clinical practice of these evidence-based recommendations, in our opinion, several considerations should be highlighted.

Surgery plus Whole Brain Radiotherapy

In this paper, the indication at the use of surgery plus whole-brain radiotherapy (WBRT) as a superior treatment modality to WBRT alone for patients with newly diagnosed BMs is supported with a "Class I" evidence, referring to previous published studies. Nevertheless, this level of evidence could be not appropriated. The three cited studies in the paper by Nahed and colleagues[1] are all retrospective and they are burdened by biases that could make the results not generalizable on the entire population subject of the proposed question.

Several years ago, NCCN guidelines reported surgery plus WBRT as a therapeutic "Class I" evidence, based on the results of first randomized trial by Patchell and colleagues and their subsequent study,[2] in which patients with a single BM were assigned to either surgical removal followed by radiotherapy (surgical group) or biopsy and radiotherapy (radiation group). The conclusion of the study reported a better overall survival (OS) in the surgery group, unfortunately the study had several criticisms, including years of the study (1985-1988) and sample size calculation (only 48 patients enrolled in the 2 groups). For these reasons, the analysis by Patchell et al[2] cannot be considered a "Class I" evidence for single BM. Furthermore, other prospective randomized trials did not show any OS benefit in patients that received surgery or radiosurgery (SRS) alone or combined with WBRT, while it's clear the upfront addition of WBRT is associated with diminished cognitive function and worse quality of life, in patients with a good performance status and OS > 6 months.[3] A systematic review by Cochrane concluded that "there is low quality evidence that adding upfront WBRT to surgery or SRS decreases any intracranial disease progression at one year and there was no clear evidence of an effect on overall and progression free survival."[4] Based on these results, the most recent NCCN guidelines do not recommend routinely the addiction of adjuvant WBRT to surgery or SRS for limited BMs

Surgery plus SRS

The assumption of adding radiation treatment to surgery in the treatment of BMs is to increase local control and to reduce or delay the onset of neurological disorders related to the progression of intracranial disease. In this scenario, there is a growing interest for the postoperative SRS. If until the last year the evidence supporting this type of therapeutic approach could be considered "Class III," today the recent results of two-randomized trials[5,6] move the scale needle towards higher levels of evidence. The primary endpoints of these trials are complementary to each other, in fact the Mahajan et al[5] showed that the administration of SRS to the resection cavity reduced significantly the local recurrence compared to observation alone; while Brown et al[6] concluded that SRS on surgical bed should be considered one of the standards of care as a less toxic alternative to WBRT for patients with good performance status, OS > 6 months and limited number of BMs treated with previous surgery.

Should Patients With Newly Diagnosed Metastatic Brain Tumors Undergo Surgery, Stereotactic Radiosurgery, or Whole Brain Radiotherapy?

Finally, this question does not find a direct recommendation. If it were clear that WBRT alone is subtherapeutic treatment approach or it should be reserved to patients with poor general status and its association with surgery or SRS could be a possible but questionable option, the real query could be: "should patients with newly diagnosed BMs undergo surgery or SRS?". Considering the decision to surgery depends on the need to establish histologic diagnosis, the lesion size and number and their location, it should be highlighted that SRS alone should be offered and preferred for patients not requiring surgery. Currently, there is no definitive evidence regarding the effectiveness and safety of surgery vs SRS in patients with single BM, and benefits must be decided on a case-by-case.[7] For patients with 2-4 BMs SRS could be the preferred choice. In the literature, no consistent data are available that compare directly SRS vs surgery. The phase III study by Kocher et al[8] that randomized patients with 1-3 BMs in good condition to 4 treatment arms (79 patients for surgery alone, 81 for surgery plus WBRT, 100 for SRS alone, and 99 for SRS plus WBRT), although the primary endpoint was the performance status deterioration between adjuvant WBRT or observation after either surgery or SRS, in the arms SRS alone and surgery alone it showed a trend of lower cumulative incidence of intracranial progression on initial site in favor of SRS alone (32 events on

100 patients in SRS alone arm vs 47 events on 79 patients in surgery alone arm).

Another equally important consideration should be argued about the efficacy of central nervous system active drugs that play a key role in the treatment of select patients, changing the "standard recommendations" in local therapy, also in case of multiple BMs.

In conclusion, the work by Nahed and colleagues[1] is worthy of praise, but, in the context of educational papers, such as guidelines or position papers, it is important to pay attention to the quality and level of evidence, highlighting that some advices should not be interpreted as a definitive indication but as a recommendation to be tailored on the individual patient and shared in a multidisciplinary context.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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06/22/2023

In Reply: Congress of Neurological Surgeons Systematic Review and Evidence-Based Practice Guidelines on the Role of Surgery in the Management of Adults With Metastatic Brain Tumors

To the Editor:

We would like to thank the authors for the Letter to the Editor[1] for their thoughtful comments on the recently reported guidelines[2] on the role of surgery in the management of adults with metastatic brain tumors. The author's points are salient and identify challenges that we encountered while drafting these guidelines and interpreting the quality of studies directed at surgical intervention and radiation management for these patients. Regarding the conclusion that there is Class I evidence to conclude surgery plus whole-brain radiotherapy (WBRT) is superior to WBRT alone, the authors critically point out limited studies from the timeframe of our guidelines that support this conclusion. An important aspect of our reported guidelines is that all studies included in our analysis had to include surgery as a therapeutic intervention. As a result, studies that looked at adjuvant WBRT to radiosurgery alone were not included in our analysis. In that context, we did not feel that there was sufficient data from the 121 studies that met our search criteria to contradict the conclusions from the first guidelines published by Kalkanis et al[3] but agree that there is emerging literature that supports the movement of clinical practice away from upfront WBRT following surgical intervention.

Regarding the use of surgery plus stereotactic radiosurgery (SRS), the data included in the guidelines were suggestive that the addition of SRS following surgery for local control was beneficial (Level 2 evidence). However, we were limited by high-quality prospective clinical trials for the time frame included in our review of the literature. The authors critically point out recently reported studies by Mahajan et al[4] and Brown et al[5] that were published after the timeframe of our guidelines that add further weight to the role of adjuvant SRS for local control following surgery. We expect that these studies will certainly provide the foundation for Level 1 recommendations in the future.

Lastly, the authors point out the challenge of limited evidence to answer the questions of upfront surgical resection vs SRS. We agree that at this time, there is no Class 1 evidence to answer this question and that the decision to proceed with upfront surgery or SRS must be made within the unique clinical context of each patient, consistent with the study by Fuentes et al.[6] As the therapeutic landscape of systemic agents continue to evolve with targeted therapies and immunotherapy, we anticipate that the role of upfront surgery and SRS will continue to evolve.

We would like to thank the authors for the letter to the editor et al for their insightful comments and areas of future investigation. As systemic control continues to improve for patient with metastatic disease, the management of intracranial progression will continue to be a pressing clinical issue. While the role of surgical intervention in this patient population continues, future studies are needed to fine-tune the recommendations regarding the optimal surgical indications, surgical timing, and adjuvant therapies amongst patients undergoing surgery for brain metastases.

Disclosures

Dr Nahed has founder shares in and serve as a consultant for REACT Neuro and perform outside consulting for companies which are not related to the subject or content of this article. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz235

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Letter: Food and Drug Administration Approval of the Wove Endobridge Device: What do the Numbers Tell Us?

To the Editor:

On December 31, 2018 Sequent Medical received FDA (US Food and Drug Administration) approval for commercialization of the Woven Endobridge Device (WEB device, Sequent Medical Inc, Aliso Viejo, California) in the United States.[1] The WEB device, an endovascular device for treatment of intracranial aneurysms,[2] is part of a new generation of medical devices for endovascular treatment of intracranial aneurysms with presumed better efficacy and extended indications.[3-6] FDA approval for a device is crucial for medical device companies to enter the market and obtain market share. The WEB device was approved for aneurysms at the *"middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex, or basilar artery apex for the endovascular treatment of adult patients with saccular, wide neck, bifurcation intracranial aneurysms with dome diameter from 3 mm to 10 mm and either neck size 4 mm or greater or the dome-to-neck ratio is greater than 1 and less than 2."*[1] The approval for the WEB device was based on a the "WEB-IT trial" which is a Premarket Approval (PMA) study that is necessary for Class III medical devices (devices that "usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury").[7,8] Of note, the WEB device has been available in Europe since 2011 as such a trial was not necessary before commercialization based on local legislation at the time there.[2] Nevertheless, the WEB device has gained some traction in several centers in Europe.[9-11]

There are, however, potential issues regarding safety, efficacy, and manner of introduction of the WEB device. Several manufacturer-sponsored single-arm prospective trials have been conducted for the WEB device to evaluate its safety and efficacy, both in the United States and Europe.[6,7,12] Unlike endovascular coiling, none of these trials made a methodologically rigid comparison with the current standard therapy for wide-neck aneurysms: clipping.[13-16] It therefore remains unclear which treatment strategy is superior with regard to functional and treatment outcomes or whether the WEB device offers any true advantages. The studies that evaluated the WEB device were conducted relatively recently and long-term outcomes are not available.[6,7,12] In the WEB-IT trial 18 out of 143 (12.6%) patients had a recurrence at 1 yr,[17] which is slightly lower compared to rates reported by European trials.[6,12] Similarly, complete occlusion was only achieved in 77 out of 143 (53.8%) patients.[17] This rate is relatively low when compared to occlusion rates from wide-neck aneurysms from the BRAT trial with 6 yr of follow-up (complete occlusion 91.8% at 6 yr for clipping).[16]

Similarly, retreatment was necessary in 8 out of 143 (5.6%)[17] patients after 1 yr in the WEB-IT trial compared to none in the BRAT trial (0 out of 136 wide-neck aneurysm patients).[16] Retreatment of previously treated intracranial aneurysm patients may be challenging and come with poor outcomes.[18] Some have suggested that retreatment of a WEB device treated aneurysm is safe and effective, but this is based on retrospective data with small numbers.[19,20] One small retrospective study that evaluated large aneurysms (≥10 mm) treated with WEB devices described a retreatment rate of 7 out of 15 patients of which 2 resulted in severe complications and one mortality.[21] One of these retreatments was surgically which proved to be extremely challenging.[21] Although the WEB device is officially not approved all types of intracranial aneurysms in the US, we fear that the recent approval might result in "off-label use" of these devices in eg large aneurysms patients. For instance, Pipeline embolization devices (Medtronic) are being used off-label for various indications.[22]

One may still argue that despite potentially inferior treatment related outcomes, functional outcomes will not be inferior as seen with coiling and clipping.[16] This is at this moment no more that speculation as long-term functional outcomes that compare the WEB device with other treatment modalities are not available. To our knowledge, no trial that aims to compare the WEB device to other treatment modalities in a methodologically sound manner is being conducted. Perhaps if the WEB device had been introduced according to the Idea, Development, Exploration, Assessment, Long-term study criteria for devices (IDEAL-D), which places an emphasis on rigorous evaluation data on outcomes, outcomes of such a trial would be available.[23,24] However, there is currently no incentive or obligation for medical device manufacturers to follow guidelines that would require more evaluation or trials, both in the US and Europe. From a manufacturer's perspective, following frameworks such as the IDEAL-D for methodological sound introduction of devices could - at least on the short term - potentially only limit shareholder value due to increased costs. There is even the possibility of no return on investment if more rigorous evaluation would result in denial of commercialization, proven inferiority to other treatment modalities, or a lack of trust in the device among physicians and patients.

Selection of the optimal treatment strategy will remain at the discretion of physicians responsible for treatment of intracranial aneurysms and physicians should take complete occlusion and potential retreatment rate into consideration. We believe the WEB device may only be useful when no proven options are deemed feasible. Physicians should familiarize themselves with the results of available trials and should present these to the patient and his or her family to come to an optimal treatment strategy.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Letter: The Indusium Griseum: Anatomic Study with Potential Application to Callosotomy

To the Editor:

We read with great interest the paper by Tubbs et al[1] describing the human indusium griseum (IG) to be a glial membrane above the corpus callosum (CC) without neuronal cells nor connections with the hippocampus. The study, carried out by magnetic resonance imaging and histological and immunohistochemical (ihc) techniques, led the Authors to conclude that transection of this membrane, unavoidable when performing callosotomy (ie, to relieve drug-resistant epilepsy), should not be the reason for the postoperative memory deficit observed in some patients.

However, our current preliminary results seem to indicate that IG contains neurons, some of them immunopositive to the neuronal nitric oxide synthase (nNOS), the enzyme responsible for the synthesis of the nitric oxide (NO).

In our study, the CC and the overlying IG were collected from 13 adult human autoptic brains without evident pathologies. The work was approved by the Research Ethics Committee of our University and conducted in line with the principles of the Helsinki Declaration of 1975, as revised in 2008. After the specimens were fixed in formalin, paraffin, or frozen

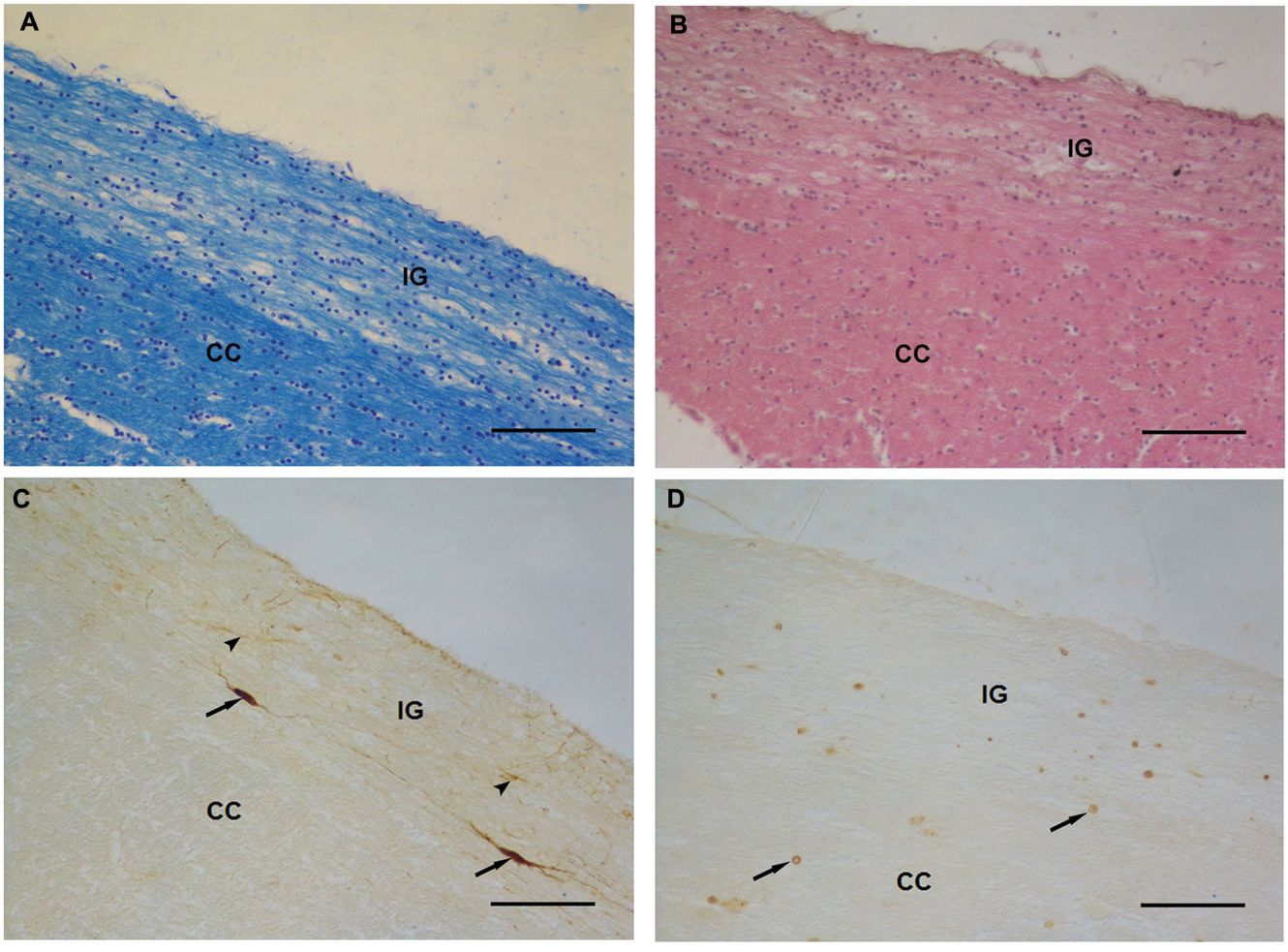


FIGURE. *Sagittal sections of IG.* **A**, **B**, *Staining of IG by Luxol fast blu* **A** *and eosin* **B**. *The identification of IG is possible thanks to the orientation of its fibers which travel perpendicularly to those of the CC.* **C**, *nNOS-positive cells (arrows) are present within the IG, often at the border with CC. Several IG areas contain nNOS-positive nerve fibers (arrowheads).* **D**, *NEUN-positive cells are distributed throughout the entire IG (arrows). Scale bars, 100 μm.*

sections were cut according to a sagittal plane along the genu of CC and overlying IG. The identification of IG in tissue sections was obtained in light microscopy by Luxol fast blue and eosin staining: both techniques mark the fibers of the IG travelling sagittally, allowing to distinguish them from those of the CC, running coronally (Figure A and B). Immunohistochemical procedure to detect nNOS and neuronal nuclear marker (NeuN) showed the presence of nNOS-positive neuronal-like cells (Figure C), and of NeuN-positive cells (Figure D). Neuronal NOS-positive neuronal-like cells displayed bipolar fusiform or rectangular morphologies, were located along rostro-caudal and medio-lateral directions, and often they were found at the boundary between IG and CC (Figure C). The lack of neurons claimed by Tubbs et al was probably due to the fact they did not use neuronal markers for their ihc analyses, being their study based on synaptophysin, neurofilament and Luxol fast blue/periodic acid-Schiff staining of IG. Our observations are in accordance with a previous Golgi study performed in rats[2] and with a very recent paper by Rasonja et al[3] demonstrating that IG in human adult brains is immunopositive to neuronal and synaptic markers. Thus, the presence of neurons and of nNOS positive neuronal-like cells in IG suggest that it is not a merely rudimentary tissue,[4] but likely plays a functional role in the adult brain. As evidenced by a recent immunohistochemical paper[5] the rat IG contains neurons expressing neurokinin-1 receptor, sending fibers to the underlying CC and to the cingulate cortex (Cg). Altogether, these observations suggest an intercommunication among IG, CC and Cg, leading to the hypothesis that CC lesioning could provoke functional detrimental effects.

Disclosures

UNIVPM (PSA 2016) to Dr Fabri. Fellowship to Dr Lorenzi was supported (60%) by PSA 2016. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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This material was presented at the 69th SIF National Congress, Italian Physiological Society, September 19-21, 2018, Florence, Italy, as a Poster.

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In Reply: The Indusium Griseum: Anatomic Study with Potential Application to Callosotomy

To the Editor:

We appreciate the interest of the authors in our previous work on this topic.[1] Of note, we performed neuronal nuclear marker (NeuN) immunostaining on all 4 indusium griseum samples, but we did not detect any neurons in our samples. In fact, we reviewed our slides again for the purpose of this response.

In addition, Figure 1C in the authors' letter[2] shows 2 neurons at the interface between the indusium griseum and corpus callosum. We can accept those as neurons from a morphologic point of view, but Figure 1D (with NeuN immunostaining) shows a smattering of positive nuclei and some nonspecific staining. These findings do not correlate with those shown in Figure 1C and are not morphologically convincing as neurons. Indeed, the stain essentially highlights everything in the image, which casts doubt on the sensitivity and specificity of the stain and the technique used. Again, we appreciate the interest of these authors in our work.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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06/22/2023

Letter: White Blood Cell Count Improves Prediction of Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage

To the Editor:

We read with great interest the article by Fawaz Al-Mufti et al[1] in your journal regarding the prediction of delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH). The results from the study suggested that white blood cell (WBC) count is a marker for prediction of DCI in aSAH patients. The authors found that WBC count $>12.1 \times 10^9$/L within 72 h of admission was predictor of DCI in good-grade (WFNS grade <3) aSAH patients. And WBC count in the first 72 h of admission was stronger than modified-Fisher score.

This article has great clinical significance, providing a trouble-free way to predict DCI following aSAH. We simply need to evaluate WBC count to predict the DCI after aSAH and determine whether the patients should be downgraded from the intensive care unit, which is cost-saving both for patients and hospitals. However, some issues still need to be discussed.

This is a single center observational cohort study, and the value of WBC count in predicting DCI following aSAH should be verified in multi-center prospective controlled trials to give more supporting evidence for its routine clinical use. In addition, the authors found that WBC count is a good predictor in good-grade aSAH patients. So, what about the poor-grade patients? Is there still a better marker for predicting both good-grade and poor-grade aSAH patients? A good biomarker should be generalizable. As mentioned in this article, the poor-grade aSAH patients experience dramatic inflammation and WBC count elevations, so WBC count is not a good marker for them. On the other hand, for patients with certain immune deficiency diseases, WBC count is not a good way to make predictions.[2] Therefore, a more specific marker is still needed.

DCI following aSAH occurs in up to 30% of patients, and it is characterized by delayed onset of cerebral ischemia, leading to motor deficits, cognitive dysfunction, and reduced quality of life.[3] Cerebral vasospasm is one of the important contributors to DCI.[4] A recent study by Vellimana et al[5] suggested that MMP-9 expression and activity increased after SAH and MMP-9 inhibition led to decreased vasospasm and neurological deficits. So, will MMP-9 might be a marker for predicting DCI after aSAH. Additionally, a recent published article by Matsumoto Atsushi et al indicated that histidine-rich glycoprotein could be a predictor of vasospasm following aSAH, but the patient number is limited (7 controls and 14 aSAH patients).[6] Further clinical research should be carried out to provide more evidence.

DCI following aSAH is a multifactorial pathophysiological process and it is of great significance to find out a specific biomarker to predict it in clinical scenarios.

Disclosures

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Letter: Long-Term Effect of Decompressive Craniectomy on Intracranial Pressure and Possible Implications for Intracranial Fluid Movements

To the Editor:

Intracranial pressure (ICP) monitoring is crucial in the management of various neurological and neurosurgical diseases such as traumatic brain injury (TBI), hydrocephalus, and intracerebral hemorrhage. However, pathological ICP (not only above, but also under reference ranges) may persist beyond the admission to the neurointensive care unit (NICU).[1] Currently, the gold standard for the measurement of ICP in TBI patients remains the external ventricular catheter. Most ICP monitoring devices in current clinical use require a physical connection between the brain and the external environment. The placement of these devices carries a significant morbidity, particularly infection, which limits the duration of monitoring. Therefore, patients undergoing repeated monitoring require multiple surgical procedures.[2] Several telemetric monitoring devices, in which data are in some way transmitted transcutaneously, have been developed over the last 30 yr. The possibility of intracranial continuous monitoring for several weeks in patients is a novel concept. The emergence of telemetric evaluation using sensors for short- and long-term monitoring is part of a new era.[3] This technique offers to neurosurgeons an overview of the changes within the cranial vault in relation to ICP and allows measurements in the patient's everyday life. Telemetric ICP monitoring is useful in patients with complicated cerebrospinal fluid (CSF) dynamic disturbances who would, otherwise, require repeated invasive pressure monitoring.[4]

We all know decompressive craniectomy (DC) is being widely used to manage refractory intracranial pressure; however, the issues related to long-term sequel and morbidity are not well addressed as well as understood. Lilja-Cyron et al[3] present an interesting study on the long-term potential of the evaluation by telemetry of ICP in patients undergoing DC and aimed at helping to define the best time for cranioplasty. Changes in the level of hydrodynamics of the CSF are a complex phenomenon, and this type of studies stimulates research in this field. The study offers us evidence confirming that ICP values continue to decrease gradually after NICU discharge from 7.8 ± 2.0 mm Hg to −1.8 ± 3.3 mm Hg ($P = .02$), reaching negative values after the third week of discharge. The most pronounced decrease occurred during the first month. DC abolishes normal intracranial fluid dynamics, ie, there was no difference between the ICP in supine and the ICP in the sitting position ($P = .67$). Pulsatile wave amplitude (PWA) was markedly reduced from initial 1.2 ± 0.7 mm Hg to 0.4 ± 0.3 mm Hg ($P = .05$). Intracranial PWA largely depends on intracranial compliance,[5] and due to the disruption of the brain's rigid enclosing following DC, it is not surprising that PWA is diminished after DC. Pulse wave propagation is believed to be an important driver of CSF flow, and emerging evidence also supports its role in other intracranial fluid movements, such as glymphatic flow.[6-8] Hence, the reduced intracranial PWA may contribute to the development of complications related to CSF flow (hygroma, hydrocephalus, and "syndrome of the trephined") occurring after DC.

"Pressure unloading" of the brain through postural ICP changes is absent following DC and that PWA, considered to be a prime driver of intracranial fluid movements, is severely diminished. These abnormalities appear very early in the postcraniectomy period and may potentially cause or worsen CSF-related complications observed after DC or directly affect the brain function. All this leads to the concerns that neurosurgeons have after DC is performed: When is the best time to perform cranioplasty?

Lilja-Cyron et al[3] have marked the lack of subgroup analyses by etiology of brain edema. That is why further investigations and studies are needed to define the right time for cranioplasty, specifically in patients with TBI, and also to determine if there is a difference in ICP change in different diseases requiring DC (TBI, acute middle cerebral artery infarct, etc).

Carrying out the cranioplasty after DC has a positive impact not only at the aesthetic level but also on the cerebral metabolism and the hydrodynamics of the CSF.[9,10] Cranioplasty remarkably improves neurological and cognitive outcomes supported by an improvement in cerebral blood perfusion.[11] Performing it early between 15 and 30 d after initial craniectomy may also minimize infection, seizure, and bone flap resorption, whereas waiting for >90 d may minimize hydrocephalus but may increase the risk of seizure.[12]

Absence of postural ICP change and reduced PWA in the postcraniectomy period support an early cranioplasty strategy, but the surgical timing must be based on an overall assessment of individual patients.[3]

The correction of the cranial defect after DC will allow us as physicians to reduce the development of complications such as trephination syndrome, hygromas, hydrocephalus, and ischemic events, all of which are a consequence of disturbances of intracranial fluid movements (CSF and/or glymphatic flow).

The telemetric ICP monitoring in the NICU and after discharge of patients with neurotrauma will most likely become a technique for comprehensive management.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Letter: Long-Term Effect of Decompressive Craniectomy on Intracranial Pressure and Possible Implications for Intracranial Fluid Movements

To the Editor:

Intracranial pressure (ICP) monitoring is crucial in the management of various neurological and neurosurgical diseases such as traumatic brain injury (TBI), hydrocephalus, and intracerebral hemorrhage. However, pathological ICP (not only above, but also under reference ranges) may persist beyond the admission to the neurointensive care unit (NICU).[1] Currently, the gold standard for the measurement of ICP in TBI patients remains the external ventricular catheter. Most ICP monitoring devices in current clinical use require a physical connection between the brain and the external environment. The placement of these devices carries a significant morbidity, particularly infection, which limits the duration of monitoring. Therefore, patients undergoing repeated monitoring require multiple surgical procedures.[2] Several telemetric monitoring devices, in which data are in some way transmitted transcutaneously, have been developed over the last 30 yr. The possibility of intracranial continuous monitoring for several weeks in patients is a novel concept. The emergence of telemetric evaluation using sensors for short- and long-term monitoring is part of a new era.[3] This technique offers to neurosurgeons an overview of the changes within the cranial vault in relation to ICP and allows measurements in the patient's everyday life. Telemetric ICP monitoring is useful in patients with complicated cerebrospinal fluid (CSF) dynamic disturbances who would, otherwise, require repeated invasive pressure monitoring.[4]

We all know decompressive craniectomy (DC) is being widely used to manage refractory intracranial pressure; however, the issues related to long-term sequel and morbidity are not well addressed as well as understood. Lilja-Cyron et al[3] present an interesting study on the long-term potential of the evaluation by telemetry of ICP in patients undergoing DC and aimed at helping to define the best time for cranioplasty. Changes in the level of hydrodynamics of the CSF are a complex phenomenon, and this type of studies stimulates research in this field. The study offers us evidence confirming that ICP values continue to decrease gradually after NICU discharge from 7.8 ± 2.0 mm Hg to −1.8 ± 3.3 mm Hg ($P = .02$), reaching negative values after the third week of discharge. The most pronounced decrease occurred during the first month. DC abolishes normal intracranial fluid dynamics, ie, there was no difference between the ICP in supine and the ICP in the sitting position ($P = .67$). Pulsatile wave amplitude (PWA) was markedly reduced from initial 1.2 ± 0.7 mm Hg to 0.4 ± 0.3 mm Hg ($P = .05$). Intracranial PWA largely depends on intracranial compliance,[5] and due to the disruption of the brain's rigid enclosing following DC, it is not surprising that PWA is diminished after DC. Pulse wave propagation is believed to be an important driver of CSF flow, and emerging evidence also supports its role in other intracranial fluid movements, such as glymphatic flow.[6-8] Hence, the reduced intracranial PWA may contribute to the development of complications related to CSF flow (hygroma, hydrocephalus, and "syndrome of the trephined") occurring after DC.

"Pressure unloading" of the brain through postural ICP changes is absent following DC and that PWA, considered to be a prime driver of intracranial fluid movements, is severely diminished. These abnormalities appear very early in the postcraniectomy period and may potentially cause or worsen CSF-related complications observed after DC or directly affect the brain function. All this leads to the concerns that neurosurgeons have after DC is performed: When is the best time to perform cranioplasty?

Lilja-Cyron et al[3] have marked the lack of subgroup analyses by etiology of brain edema. That is why further investigations and studies are needed to define the right time for cranioplasty, specifically in patients with TBI, and also to determine if there is a difference in ICP change in different diseases requiring DC (TBI, acute middle cerebral artery infarct, etc).

Carrying out the cranioplasty after DC has a positive impact not only at the aesthetic level but also on the cerebral metabolism and the hydrodynamics of the CSF.[9,10] Cranioplasty remarkably improves neurological and cognitive outcomes supported by an improvement in cerebral blood perfusion.[11] Performing it early between 15 and 30 d after initial craniectomy may also minimize infection, seizure, and bone flap resorption, whereas waiting for >90 d may minimize hydrocephalus but may increase the risk of seizure.[12]

Absence of postural ICP change and reduced PWA in the postcraniectomy period support an early cranioplasty strategy, but the surgical timing must be based on an overall assessment of individual patients.[3]

The correction of the cranial defect after DC will allow us as physicians to reduce the development of complications such as trephination syndrome, hygromas, hydrocephalus, and ischemic events, all of which are a consequence of disturbances of intracranial fluid movements (CSF and/or glymphatic flow).

The telemetric ICP monitoring in the NICU and after discharge of patients with neurotrauma will most likely become a technique for comprehensive management.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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10.1093/neuros/nyz275