CONTENTS

Letters to the Editor published online

The illustration on the cover of this issue is taken from the article by Nicholas J. Salgia, Paulo G. Bergerot, Manuel Caitano Maia, Nazli Dizman, JoAnn Hsu, John D. Gillece, Megan Folkerts, Lauren Reining, Jeffrey Trent, Sarah K. Highlander and Sumanta K. Pal, Stool Microbiome Profiling of Patients with Metastatic Renal Cell Carcinoma Receiving Anti–PD-1 Immune Checkpoint Inhibitors, which is published on pp. 498–502 of this issue.

CONGRESS CALENDAR

1.10–2.10.2020 **Moscow** Russia	15th Annual Congress of the Russian Association of Oncological Urology	**Contact:** Russian Association of Oncological Urology Tel.: +7 495 6452199 E-mail: roou@roou.ru Website: www.roou.ru
1.10–4.10.2020 **Thessaloniki** Greece	25th Pan-Hellenic Urological Congress	**Contact:** Hellenic Urological Association Tel.: + 30 210 7223126 E-mail: hua@huanet.gr Website: www.huacongress.gr
2.10.2020 **Virtual online course**	ESU course on Upper Tract Laparoscopic Surgery to be held during the National Congress of the Albanian Association of Urologic Surgeons	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education
3.10.2020 **Virtual online course**	ESU course on Upper Tract Laparoscopic Surgery to be held during the National Congress of the Hellenic Urological Association	**Contact:** Newcastle Surgical Training Centre, Freeman Hospital Tel.: +44 191 2138628 E-mail: lucy.thomas@nuth.nhs.uk Website: www.nstcsurg.org
5.10–6.10.2020 **Newcastle upon Tyne** UK	PCNL Masterclass Course	**Contact:** Société Internationale d'Urologie (SIU) E-mail: congress@siu-urology.org Website: www.siu-urology.org
7.10–11.10.2020 **Montreal** Canada	40th Congress of Société Internationale d'Urologie	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education/
15.10.2020 **Virtual online course**	ESU course on Treatment of Oligometastatic Cancer	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org
15.10–17.10.2020 **Lublin** Poland	II International Congress of Minimally Invasive Surgery	**Contact:** Wydawnictwo Czelej Sp. z o.o. Tel.: +48 664 424105 E-mail: lukasz.nowak@czelej.com.pl Website: http://www.kongreschmi.eu
21.10.2020 **Virtual online course**	7th Confederación Americana de Urologia Residents Education Programme (CAUREP)	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org
22.10.2020 **Virtual online course**	ESU course on Dealing with the Challenge of Infections in Urology to be held during the National Congress of the Tunisian Urological Society	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education
26.10–28.10.2020 **Dundee** UK	Rectal Prolapse Surgical Management Cadaveric Course	**Contact:** The Dundee Institute for Healthcare Simulation Tel.: +44 (1382 383400 E-mail: smccomiskie@dundee.ac.uk Website: https://dihs.dundee.ac.uk/
28.10–29.10.2020 **Nijmegen** The Netherlands	ESU-ESFFU Masterclass on Functional Urology	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org

29.10.2020 **Poznan** Poland	ESU course on Urinary Incontinence in Children and Adults to be held during the National Congress of the Polish Urological Association	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education/
29.10–30.10.2020 **Barcelona** Spain	ESU-ESFFU Masterclass on Functional Urology	**Contact:** European School of Urology (ESU) Tel.: +31 26 36890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.uroweb.org/
30.10–31.10.2020 **Virtual online meeting**	ELUTS20: The European Lower Urinary Tract Symptoms meeting	**Contact:** Congress Consultants BV Tel.: +31 26 3891751 Website: eluts20.org
5.11–7.11.2020 **Virtual online meeting**	17th Meeting of the EAU Robotic Urology Section in conjunction with 12th German Society Robotic Urology	**Contact:** Congress Consultants BV Tel.: 026 389 1751 E-mail: erus@congressconsultants.com Website: www.erus20.org
9.11–11.11.2020 **Birmingham** UK	Oncology Convention (new date)	**Contact:** Roar B2B Website: www.oncologyconvention.com
9.11–11.11.2020 **Birmingham** UK	Annual Meeting of the British Association of Urological Surgeons	**Contact:** British Association of Urological Surgeons Email: admin@baus.org.uk Website: www.baus.org.uk
12.11.2020 **Athens** Greece	ESU course on Oligometastases in Genitourinary Cancers to be held during the 12th European Multidisciplinary Meeting on Urological Cancers (EMUC)	**Contact:** Congress Consultants BV Tel.: +31 26 3891751 E-mail: erus@congressconsultants.com Website: http://www.erus20.org
12.11.2020 **Athens** Greece	9th Meeting of the EAU Section of Urological Imaging	**Contact:** European School of Urology Tel.: +31 26 3890680 Email: esu@uroweb.org Website: www.uroweb.org/education
12.11–15.11.2020 **Virtual online meeting**	12th European Multidisciplinary Congress on Urological Cancers (EMUC20)	**Contact:** Congress Consultants BV Tel.: +31 26 3891751 E-mail: emuc@congressconsultants.com Website: www.emuc20.org
14.11.2020 **Limassol** Cyprus	ESU course on Diagnostic and Therapeutic Management of Male Infertility to be held during the National Congress of the Cyprus Urological Association	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education
18.11–21.11.2020 **Las Vegas** USA	50th Annual Meeting of the International Continence Society	**Contact:** International Continence Society (ICS) Website: www.ics.org/2020
19.11–20.11.2020 **Barcelona** Spain	ESU-ESUT Masterclass on Lasers in Urology	**Contact:** European School of Urology (ESU) Tel.: +31 26 36890680 E-mail: w.dennissen@uroweb.org Website: https://esu-masterclasses.uroweb.org/
20.11.2020 **Virtual online course**	ESU course on Update in Bladder and Prostate Cancer to be held during the National Congress of the Turkish Association of Urology	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.uroweb.org/education
25.11.2020 **Virtual online course**	ESU course on Tips and Tricks in Challenging Surgeries to be held during the National Congress of the Spanish Urological Association	**Contact:** European School of Urology Tel.: +31 26 3890680 Email: esu@uroweb.org Website: www.uroweb.org/education

26.11–27.11.2020 **Marseille** France	ESU-ESUI Masterclass on Prostate Biopsy	**Contact:** European School of Urology Tel.: +31 26 3890680 Website: https://esu-masterclasses.uroweb.org/
2.12–4.12.2020 **Berlin** Germany	Art in Flexible - Step 1 (postponed)	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: r.vanloenen@uroweb.org Website: www.artinflexible.uroweb.org
9.12–12.12.2020 **Munster** Germany	International Congress of Andrology	**Contact:** Conventus Congressmanagement & Marketing GmbH E-mail: registrierung@conventus.de Website: www.andrology2020.de/
1.2–3.2.2021 **Hurghada** Egypt	18th Annual Meeting of the Pan Arab Continence Society	**Contact:** Pan Arab Continence Society E-mail: msmourad@icloud.com Website: www.pacs.org.eg/
4.2–5.2.2021 **Prague** Czech Republic	ESU-ESOU Masterclass on Non–Muscle-Invasive Bladder Cancer	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.uroweb.org
12.2–13.2.2020 **Gothenburg** Sweden	27th Meeting of the EAU Section of Urological Research (ESUR21) in collaboration with the EAU Section of Uropathology (ESUP)	**Contact:** Congress Consultants BV Website: www.esur21.org
12.2–14.2.2020 **Gothenburg** Sweden	18th Meeting of the European Section of Oncological Urology	**Contact:** Congress Consultants BV Website: https://esou.uroweb.org/
16.2–20.2.2021 **Rotterdam** The Netherlands	Annual Congress of the European Society for Sexual Medicine 2021	**Contact:** European Society for Sexual Medicine E-mail: admin@essm.org Website: https://www.essm.org
8.4–9.4.2020 **Amsterdam** The Netherlands	ESU-ESOU Masterclass on Muscle-Invasive Bladder Cancer	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org
15.4–17.4.2021 **Berlin** Germany	URO Berlin Skills Teaching and Training	**Contact:** EAU Tel.: +31 26 3890680 E-mail: m.vandewiel@uroweb.org Website: https://urobestt.uroweb.org/
28.5–29.5.2021 **Minsk** Belarus	7th Baltic Meeting in conjunction with the EAU	**Contact:** European Association of Urology Tel.: +31 26 3890680 E-mail: baltic@uroweb.org Website: https://baltic.uroweb.org
7.10–9.10.2021 **Lugano** Switzerland	Advanced Prostate Cancer Consensus Conference (APCCC)	**Contact:** Congrex Switzerland Ltd. Tel.: +41 61 6867777 E-mail: Secretariat.APCCC@congrex.com Website: https://www.apccc.org/apccc2019.html

EUROPEAN UROLOGY
James Catto, Editor-in-Chief
Academic Urology Unit, University of Sheffield
The Medical School
Beech Hill Road, Sheffield S10 2RX, UK
E-mail: platinum@europeanurology.com
Tel: +31 26 389 0680; Fax: +44 114 271 2268

EUROPEAN UROLOGY

The Platinum Hall of Fame is online only at http://www.sciencedirect.com/science/journal/03022838/78/4

Official Journal of the European Association of Urology

Official Journal of Società Italiana di Urologia (SIU)

European Board of Urology

EUROPEAN UROLOGY
James Catto, Editor-in-Chief
Academic Urology Unit, University of Sheffield
The Medical School
Beech Hill Road, Sheffield S10 2RX, UK
E-mail: platinum@europeanurology.com
Tel: +31 26 389 0680; Fax: +44 114 271 2268

EUROPEAN UROLOGY

The Platinum Hall of Fame

European Urology would like to recognize the award-winning authors and exceptional reviewers who ensure that 'your' platinum journal remains a cut above the rest.

Best Scientific Paper Prizes 2000 to the Present

2000

Laparoscopic Radical Prostatectomy: Technical and Early Oncological Assessment of 40 Operations

B. Guillonneau, X. Cathelineau, E. Barret, F. Rozet, G. Vallancien
European Urology 1999;36:14–20

2001

RPLND or Primary Chemotherapy in Clinical Stage IIA/B Nonseminomatous Germ Cell Tumors? Results of a Prospective Multicenter Trial Including Quality of Life Assessment

L. Weissbach, R. Bussar-Maatz, H. Flechtner, U. Pichlmeier, M. Hartmann, L. Keller
European Urology 2000;37:582–594

2002

Nonrandomized Comparison of Open Flank versus Laparoscopic Nephrectomy in 249 Patients with Benign Renal Disease

P. Fornara, C. Doehn, H.-J. Friedrich, D. Jocham
European Urology 2001;40:24–31

2003

Laparoscopic Dismembered Pyeloplasty – The Method of Choice in the Presence of an Enlarged Renal Pelvis and Crossing Vessels

I.A. Türk, J.W. Davis, B. Winkelmann, S. Deger, F. Richter, M.D. Fabrizio, B. Schönberger, G.H. Jordan, S.A. Loening
European Urology 2002;42:268–275

2004

The Side Effects of Bacillus Calmette-Guérin in the Treatment of Ta T1 Bladder Cancer do not Predict its Efficacy: Results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial

R.J. Sylvester, A.P.M. Van Der Meijden, W. Oosterlinck, W. Hoeltl, A.V. Bono
European Urology 2003;44:423–428
&

Maintenance Bacillus Calmette-Guérin for Ta T1 Bladder Tumors is not Associated with Increased Toxicity: Results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial

A.P.M. Van Der Meijden, R.J. Sylvester, W. Oosterlinck, W. Hoeltl, A.V. Bono
European Urology 2003;44:429–434

2005

DD3^{A3} RNA Analysis in Urine – A New Perspective for Detecting Prostate Cancer

M. Tinzl, M. Marberger, S. Horvath, C. Chypre
European Urology 2004;46:182–186

2006

Prevalence of Asymptomatic Coronary Artery Disease in Men with Vasculogenic Erectile Dysfunction: A Prospective Angiographic Study

C. Vlachopoulos, K. Rokkas, N. Ioakeimidis, C. Aggeli, A. Michaelides, G. Roussakis, C. Fassoulakis, A. Askitis, C. Stefanadis
European Urology 2005;48:996–1002

2007

Excellent Long-Term Cancer Control with Elective Nephron-Sparing Surgery for Selected Renal Cell Carcinomas Measuring More Than 4 cm

F. Becker, S. Siemer, M. Hack, U. Humke, M. Ziegler, M. Stöckle
European Urology 2006;49:1058–1064
&

Elective Nephron-Sparing Surgery Should Become Standard Treatment for Small Unilateral Renal Cell Carcinoma: Long-term Survival Data of 216 Patients

F. Becker, S. Siemer, U. Humke, M. Hack, M. Ziegler, M. Stöckle
European Urology 2006;49:308–313

2008

Morbidity and Clinical Outcome of Nephron-Sparing Surgery in Relation to Tumour Size and Indication

J.-J. Patard, A.J. Pantuck, M. Crepel, J.S. Lam, L. Bellec, B. Albouy, D. Lopes, J.-C. Bernhard, F. Guillé, B. Lacroix, A. De La Taille, L. Salomon, C. Pfister, M. Soulié, J. Tostain, J.-M. Ferriere, C.C. Abbou, M. Colombel, A.S. Belldegrun
European Urology 2007;52:148–154

2009

The Template of the Primary Lymphatic Landing Sites of the Prostate Should Be Revisited: Results of a Multimodality Mapping Study

A. Mattei , F.G. Fuechsel, N. Bhatta Dhar, S.H. Warncke, G.N. Thalmann, T. Krause, U.E. Studer
European Urology 2008;53:118–125

2010

Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) Classification of Renal Tumours in Patients who are Candidates for Nephron-Sparing Surgery

V. Ficarra, G. Novara, S. Secco, V. Macchi, A. Porzionato, R. De Caro, W. Artibani
European Urology 2009;56:786–793
Sponsored By Elsevier

2011

Positive Surgical Margin Appears to Have Negligible Impact on Survival of Renal Cell Carcinomas Treated by Nephron-Sparing Surgery

K. Bensalah, A.J. Pantuck, N. Rioux-Leclercq, R. Thuret, F. Montorsi, P. Karakiewicz, N. Mottet, L. Zini, R. Bertini, L. Salomon, A. Villers, M. Soulie, L. Bellec, P. Rischmann, A. De La Taille, R. Avakian, M. Crepel, J. Ferriere, J. Bernhard, T. Dujardin, et al.
European Urology 2010;57:466–473
Sponsored By Elsevier

http://dx.doi.org/10.1016/j.eururo.2020.08.029

EUROPEAN UROLOGY

The Platinum Hall of Fame

2012

Pentafecta: A New Concept for Reporting Outcomes of Robot-Assisted Laparoscopic Radical Prostatectomy

V. Patel, A. Sivaraman, R. Coelho, S. Chauhan, K. Palmer, M. Orvieto, I. Camacho, G. Coughlin, B. Rocco
European Urology 2011;59:702–707

2013

Pathologic Downstaging Is a Surrogate Marker for Efficacy and Increased Survival Following Neoadjuvant Chemotherapy and Radical Cystectomy for Muscle-Invasive Urothelial Bladder Cancer

R. Rosenblatt, A. Sherif, E. Rintala, R. Wahlqvist, A. Ullén, M. Nilsson, P.-U. Malmström, the Nordic Urothelial Cancer Group
European Urology 2012;61:1229–1238

2014

Final Results of an EORTC-GU Cancers Group Randomized Study of Maintenance Bacillus Calmette-Guérin in Intermediate- and High-risk Ta, T1 Papillary Carcinoma of the Urinary Bladder: One-third Dose Versus Full Dose and 1 Year Versus 3 Years of Maintenance

J. Oddens, M. Brausi, R. Sylvester, A. Bono, C. van de Beek, G. van Andel, P. Gontero, W. Hoeltl, L. Turkeri, S. Marreaud, S. Collette, W. Oosterlinck
European Urology 2013;63:462–472

2015

Bacillus Calmette-Guérin Strain Differences Have an Impact on Clinical Outcome in Bladder Cancer Immunotherapy

C.A. Rentsch, F.D. Birkhäuser, C. Biot, J.R. Gsponer, A. Bisiaux, C. Wetterauer, M. Lagranderie, G. Marchal, M. Orgeur, C. Bouchier, A. Bachmann, M.A. Ingersoll, R. Brosch, M.L. Albert, G.N. Thalmann
European Urology 2014;66:677–688

2016

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

N.D. James, M.R. Spears, N.W. Clarke, D.P. Dearnaley, J.S. De Bono, J. Gale, J. Hetherington, P.J. Hoskin, R.J. Jones, R. Laing, J.F. Lester, D. McLaren, C.C. Parker, M.K.B. Parmar, A.W.S. Ritchie, J.M. Russell, R.T. Strebel, G.N. Thalmann, M.D. Mason, M.R. Sydes
European Urology 2015;67:1028–1038

2017

A Randomized Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy

E. Baco, E. Rud, L.M. Eri, G. Moen, L. Vlatkovic, A. Svindland, H.B. Eggesbø, O. Ukimura
European Urology 2016;69:149–156

2018

Diagnostic Pathway with Multiparametric Magnetic Resonance Imaging Versus Standard Pathway: Results from a Randomized Prospective Study in Biopsy-naïve Patients with Suspected Prostate Cancer

F. Porpigalia, M. Manfredi, F. Mele, M. Cossu, E. Bollito, A. Veltri, S. Cirillo, D. Regge, R. Faletti, R. Passera, C. Fiori, S. De Luca
European Urology 2017;72:282–8

2019

Value of an Immediate Intravesical Instillation of Mitomycin C in Patients with Non–muscle-invasive Bladder Cancer: A Prospective Multicentre Randomised Study in 2243 patients

J. Bosschieter, J.A. Nieuwenhuijzen, T. van Ginkel, A.N. Vis, B. Witte, D. Newling, G.M.A. Beckers, R.J.A. van Moorselaar
European Urology, Vol. 73, Issue 2, p226–232

2020

Genomic Drivers of Poor Prognosis and Enzalutamide Resistance in Metastatic Castration-resistant Prostate Cancer

William S. Chen, Rahul Aggarwal, Li Zhang, Shuang G. Zhao, George V. Thomas, Tomasz M. Beer, David A. Quigley, Adam Foyea, Denise Playdlea,, Jiaoti Huang, Paul Lloyd, Eric Lu, Duanchen Sun, Xiangnan Guan, Matthew Rettig, Martin Gleave, Christopher P. Evans, Jack Youngren, Lawrence True, Primo Lara, Vishal Kothari, Zheng Xia, Kim N. Chj, Robert E. Reiter, Christopher A. Maher, Felix Y. Feng, Eric J. Small, Joshi J. Alumkal on behalf of the West Coast Prostate Cancer Dream Team
European Urology, Vol 76, Issue 5, p562–571

Best Scientific Paper on Fundamental Research

2007

Frozen Section for the Management of Intraoperatively Detected Palpable Tumor Lesions During Nerve-Sparing Scheduled Radical Prostatectomy

C. Eichelberg, A. Erbersdobler, A. Haese, T. Schlomm, F.K.H. Chun, E. Currlin, J. Walz, T. Steuber, M. Graefen, H. Huland
European Urology 2006;49:1011–1018

2008

Use of Haemostatic Agents and Glues during Laparoscopic Partial Nephrectomy: A Multi-Institutional Survey from the United States and Europe of 1347 Cases

A. Breda, S.V. Stepanian, J.S. Lam, J.C. Liao, I.S. Gill, J.R. Colombo, G. Guazzoni, M.D. Stifelman, K.T. Perry, A. Celia, G. Breda, P. Fornara, S.V. Jackman, A. Rosales, J. Palou, M. Grasso, V. Pansadoro, V. Disanto, F. Porpiglia, C. Milani, C.C. Abbou, R. Gaston, G. Janetschek, N.A. Soomro, J.J. De la Rosette, P.M. Laguna, P.G. Schulam
European Urology 2007;52:798–803

2009

Predictive Factors for Progression in Patients with Clinical Stage T1a Prostate Cancer in the PSA Era

A. Descazeaud, M. Peyromaure, A. Salin, D. Amsellem-Ouazana, T. Flam, A. Viellefond, B. Debré, M. Zerbib
European Urology 2008;53:355–362

2010

Should All Patients with Non–Muscle-Invasive Bladder

EUROPEAN UROLOGY

The Platinum Hall of Fame

Cancer Receive Early Intravesical Chemotherapy after Transurethral Resection? The Results of a Prospective Randomised Multicentre Study
S. Gudjónsson, L. Adell, F. Merdasa, R. Olsson, B. Larsson, T. Davidsson, J. Richthoff, G. Hagberg, M. Grabe, P.O. Bendahl, W. Månsson, F. Liedberg
European Urology 2009;55:773–780
Sponsored By Eli Lilly

2011

Complications in 2200 Consecutive Laparoscopic Radical Prostatectomies: Standardized Evaluation and Analysis of Learning Curves
M. Hruza, H. Weiß, G. Pini, A. Goezen, M. Schulze, D. Teber, J. Rassweiler
European Urology 2010;58:733–741
Sponsored by Elsevier

2012

Salvage Radical Prostatectomy for Radiation-recurrent Prostate Cancer: A Multi-institutional Collaboration
D. Chade, S. Shariat, A. Cronin, C. Savage, J. Karnes, M. Blute, A. Briganti, F. Montorsi, H. van der Poel, H. Van Poppel, S. Joniau, G. Godoy, A. Hurtado-Coll, M. Gleave, M. Dall'Oglio, M. Srougi, P. Scardino, J. Eastham
European Urology 2011;60:205–210

2013

Stage-Specific Impact of Tumor Location on Oncologic Outcomes in Patients With Upper and Lower Tract Urothelial Carcinoma Following Radical Surgery
M. Rink, B. Ehdaie, E.K. Cha, D.A. Green, P.I. Karakiewicz, M. Babjuk, V. Margulis, J.D. Raman, R.S. Svatek, H. Fajkovic, R.K. Lee,
G. Novara, J. Hansen, S. Daneshmand, Y. Lotan, W. Kassouf, H.-M. Fritsche, A. Pycham, M. Fisch, D.S. Scherr, S.F. Shariat, for the Bladder Cancer Research Consortium (BCRC) and for the Upper Tract Urothelial Carcinoma Collaboration (UTUCC)
European Urology 2012;62:677–684

2014

Natural History of Early, Localized Prostate Cancer: A Final Report from Three Decades of Follow-up
M. Popiolek, J.R. Rider, O. Andrén, S.-O. Andersson, L. Holmberg, H.-O. Adami, J.-E. Johansson
European Urology 2013;63:428–435

2015

Targeted Prostate Cancer Screening in BRCA1 and BRCA2 Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study
E.K. Bancroft, E.C. Page, E. Castro, H. Lilja, A. Vickers, D. Sjoberg, M. Assel, C.S. Foster, G. Mitche, K. Drew, L. Mæhle, K. Axcrona, D.G. Evans, B. Bulman, D. Eles, D. McBride, C. van Asperen, H. Vasen, L.A. Kiemeney, J. Ringelberg, C. Cybulski, D. Wokolorczyk, C. Selkirk, P.J. Hulick, A. Bojesen, A.-B. Skytte, Jiy Lam, L. Taylor, R. Oldenburg, R. Cremers, G. Verhaegh, W.A. van Zelst-Stams, J.C. Oosterwijk, I. Blanco, M. Salinas, Jackie Ck, D.J. Rosario, S. Buys, T. Conner, M.G. Ausems, K.-r. Ong, J. Homan, S. Domchek, J. Powers, M.R. Teixeira, S. Maia, W.D. Foulkes, N. Taherian, M. Ruijs, A.T. Helderman-van den Enden, L. Izatt, R. Davidson, M.A. Adank, L. Walker, R. Schmutzler, K. Tucker, J. Kirk, S. Hodgson, M. Harris, F. Douglas, G.J. Lindeman, J. Zgajnar, M. Tischkowitz, V.E. Clowes, R. Susman, T. Ramón y Cajal, N. Patcher, N. Gadea, A. Spigelman, T. van Os, A. Liljegren, L. Side, C. Brewer, A.F. Brady, A. Donaldson, V. Stefansdottir, E. Friedman, R. Chen-Shtoyerman, D.J. Amor, L. Copakova, J. Barwell, V.N. Giri, V. Murthy, N. Nicolai, S.-H. Teo, L. Grnhalgh, S. Strom, A. Henderson, J. McGrath, D. Gallagher, N. Aaronson, A. Ardern-Jones, C. Bangma, D. Dearnaley, P. Costello, J. Eyfjord, J. Rothwell, A. Falconer, H. Gronberg, F.C. Hamdy, O. Johannsson, V. Kh, Z. Kote-Jarai, J. Lubinski, U. Axcrona, J. Melia, J. McKinley, A.V. Mitra, C. Moynihan, G. Rennert, M. Suri, P. Wilson, E. Killick, The IMPACT Collaborators, S. Moss, R.A. Eeles
European Urology 2014;66:489–499

2016

Molecular Characterization of Enzalutamide-treated Bone Metastatic Castration-resistant Prostate Cancer
E. Efstathiou, M. Titus, S. Wen, A. Hoang, M. Karlou, R. Ashe, S.M. Tu, A. Aparicio, P. Troncoso, J. Mohler, C.J. Logothetis
European Urology 2015;6:53–60

2017

Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men
A.E. Ross, M.H. Johnson, K. Yousefi, E. Davicioni, G.J. Netto, L. Marchionni, H.L. Fedor, S. Glavaris, V. Choeurng, C. Buerki, N. Erho, L.L. Lam, E.B. Humphreys, S. Faraj, S.M. Bezerra, M. Han, A.W. Partin, B.J. Trock, E.M. Schaeffer
European Urology 2016;69:157–165

2018

SRRM4 Drives Neuroendocrine Transdifferentiation of Prostate Adenocarcinoma Under Androgen Receptor Pathway Inhibition
Y. Li, N. Donme, C. Sahinalp, N. Xie, Y. Wang, H. Xue, F. Mo, H. Beltran, M. Gleave, Y. Wang, C. Collins, X. Dong
European Urology 2017;71:68–78

2019

Intravesical Activation of the Cation Channel TRPV4 Improves Bladder Function in a Rat Model for Detrusor Underactivity
Y. Deruyver, E. Weyne, K. Dewulf, R. Rietjens, S. Pinto, N. Van Ranst, J. Franken, M. Vanneste, M. Albersen, T. Gevaert, R. Vennekens, D. De Ridder, T. Voets, W. Everaerts
European Urology, Vol. 74, Issue 3, p336–345

2020

Antifibrotic Synergy Between Phosphodiesterase Type 5 Inhibitors and Selective Oestrogen Receptor Modulators in Peyronie's Disease Models
Marcus M. Ilg , Marta Mateus , William J. Stebbeds , Uros Milenkovic,

EUROPEAN UROLOGY

The Platinum Hall of Fame

Nim Christopher, Asif Muneer, Maarten Albersen, David J. Ralph, Selim Cellek
European Urology, Vol. 75, Issue 2, Pages p329–340

Best Scientific Paper on Clinical Research

2007

Depressed Contractile Responses to Neurokinin A in Idiopathic but not Neurogenic Overactive Human Detrusor Muscle
D.J. Sellers, C.R. Chapple, D.P.W. Hay, R. Chess-Williams
European Urology 2006;49:510–518

2008

Effects of the M3 Receptor Selective Muscarinic Antagonist Darifenacin on Bladder Afferent Activity of the Rat Pelvic Nerve
K. Iijima, S. De Wachter, J.-J. Wyndaele
European Urology 2007;52:842–849

2009

Marked Gene Transcript Level Alterations Occur Early During Radical Prostatectomy
T. Schlomm, E. Näkel, A. Lübke, A. Buness, F.K.-H. Chun, T. Steuber, M. Graefen, R. Simon, G. Sauter, A. Poustka, H. Huland, A. Erbersdobler, H. Sültmann, O.J.C. Hellwinkel
European Urology 2008;53:333–346

2010

Characteristics of Spontaneous Activity in the Bladder Trigone
A. Roosen, C. Wu, G. Sui, R.A. Chowdhury, P.M. Patel, C.H. Fry
European Urology 2009;56:346–354
Sponsored By Elsevier

2011

Stem Cell Characteristics in Prostate Cancer Cell Lines
M.J. Pfeiffer, J.A. Schalken
European Urology 2010;57:246–255
Sponsored By Elsevier

2012

Transplantation of Autologous Differentiated Urothelium in an Experimental Model of Composite Cystoplasty
A. Turner, R. Subramanian, D. Thomas, J. Hinley, S. Abbas, J. Stahlschmidt, J. Southgate
European Urology 2011;59:447–454

2013

Genome-wide Analysis of CpG Island Methylation in Bladder Cancer Identified TBX2, TBX3, GATA2, and ZIC4 as pTa-Specific Prognostic Markers
R. Kandimalla, A.A.G. van Tilborg, L.C. Kompier, D.J.P.M. Stumpel, R.W. Stam, C.H. Bangma, E.C. Zwarthoff
European Urology 2012;61:1245–1256

2014

Indium-111-labeled Girentuximab ImmunoSPECT as a Diagnostic Tool in Clear Cell Renal Cell Carcinoma
C.H.J. Muselaers, O.C. Boerman, E. Oosterwijk, J.F. Langenhuijsen, W.J.G. Oyen, P.F.A. Mulders
European Urology 2013;63:1101–1106

2015

Renal Function After Nephron-sparing Surgery Versus Radical Nephrectomy: Results from EORTC Randomized Trial 30904
E. Scosyrev, E.M. Messing, R. Sylvester, S. Campbell, H. Van Poppel
European Urology 2014;65:372–377

2016

Combination Treatment with Mirabegron and Solifenacin in Patients with Overactive Bladder: Efficacy and Safety Results from a Randomised, Double-blind, Dose-ranging, Phase 2 Study (Symphony)
P. Abrams, C. Kelleher, D. Staskin, T. Rechberger, R. Kay, R. Martina, D. Newgreen, A. Paireddy, R. van Maanen, A. Ridder
European Urology 2015:67:577–588

2017

PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2
J.C. Weinreb, J.O. Barentsz*, P.L. Choyk, F. Cornu, M.A. Haider, K.J. Macur, D. Margolis, M.D. Schnall, F. Shtern, C.M. Tempany, H.C. Thoeny, S. Verma*
European Urology 2016;69:16–40
** These authors share first authorship.*

2018

CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma
B. Escudier, P. Sharma, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, H. Gurney, F. Donskov, K. Peltola, J. Wagstaff, T.C. Gauler, T. Ueda, H. Zhao, I.M. Waxman, R.J. Motzer, on behalf of the CheckMate 025 investigators
European Urology 2017;72:962–71

2019

Metabolic Biosynthesis Pathways Identified from Fecal Microbiome Associated with Prostate Cancer
M.A. Liss, J.R. White, M. Goros, J. Gelfond, R. Leach, T. Johnson-Pais, Z. Lai, E. Rourke, J. Basler, D. Ankerst, D.P. Shah
European Urology, Vol. 74, Issue 5, p575–582

2020

Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial
Jürgen E. Gschwend, Matthias M. Heck, Jan Lehmann, Herbert Rübben, Peter Albers, Johannes M. Wolff, Detlef Frohneberg, Patrick de Geeter, Axel Heidenreich, Tilman Kälble, Michael Stöckle, Thomas Schnöller, Arnulf Stenzl,, Markus Müller, Michael Truss, Stephan Roth, Uwe-Bernd Liehr, Joachim Leißner, Thomas Bregenzer, Margitta Retz
European Urology, Vol 75, Issue 4, p604–611

EUROPEAN UROLOGY

The Platinum Hall of Fame

Residents' Corner

2008

Initial Biopsy Outcome Prediction—Head-to-Head Comparison of a Logistic Regression-Based Nomogram versus Artificial Neural Network
F.K.-H. Chun, M. Graefen, A. Briganti, A. Gallina, J. Hopp, M.W. Kattan, H. Huland, P.I. Karakiewicz
European Urology 2007;51:1236–1243

&

hK2 and Free PSA, a Prognostic Combination in Predicting Minimal Prostate Cancer in Screen-Detected Men within the PSA Range 4–10 ng/ml
R. Raaijmakers, S.H. de Vries, B.G. Blijenberg, M.F. Wildhagen, R. Postma, C.H. Bangma, C. Darte, F.H. Schröder
European Urology 2007;52:1358–1364

2009

Evaluation of Prostate Cancer Detection with Ultrasound Real-Time Elastography: A Comparison with Step Section Pathological Analysis after Radical Prostatectomy
G. Salomon, J. Köllerman, I. Thederan, F.K.H. Chun, L. Budäus, T. Schlomm, H. Isbarn, H. Heinzer, H. Huland, M. Graefen
European Urology 2008;54:1354–1362

&

Radical Prostatectomy for Incidental (Stage T1a–T1b) Prostate Cancer: Analysis of Predictors for Residual Disease and Biochemical Recurrence
U. Capitanio, V. Scattoni, M. Freschi, A. Briganti, A. Salonia, A. Gallina, R. Colombo, P.I. Karakiewicz, P. Rigatti, F. Montorsi
European Urology 2008;54:118–125

2010

Influence of Nerve Transsections and Combined Bladder Filling on Intravesical Electrostimulation-Induced Bladder Contraction in the Rat
L. De Bock, S. De Wachter, J.J. Wyndaele
European Urology 2009;56:527–533
Sponsored By Eli Lilly

&

The Role of Biopsy Core Number in Selecting Prostate Cancer Patients for Active Surveillance
M. Ploussard, E. Xylinas, L. Salomon, Y. Allory, D. Vordos, A. Hoznek, C.-C. Abbou, A. de la Taille
European Urology 2009;56:891–898
Sponsored By Eli Lilly

2011

Midterm Prospective Evaluation of TVT-Secur Reveals High Failure Rate
J.N. Cornu, P. Sèbe, L. Peyrat, C. Ciofu, O. Cussenot, F. Haab
European Urology 2010;58:157–161

&

HYAL-1 Hyaluronidase: A Potential Prognostic Indicator for Progression to Muscle Invasion and Recurrence in Bladder Cancer
M.W. Kramer, R. Golshani, A.S. Merseburger, J. Knapp, A. Garcia, J. Hennenlotter, R.C. Duncan, M.S. Soloway, M. Jorda, M.A. Kuczyk, A. Stenzl, V.B. Lokeshwar
European Urology 2010;57:86–94

2012

Exosomes as Biomarker Treasure Chests for Prostate Cancer
D. Duijvesz, T. Luider, C. Bangma, G. Jenster
European Urology 2011;59:823–831

&

Cancer-Specific and Other-Cause Mortality After Radical Prostatectomy Versus Observation in Patients with Prostate Cancer: Competing-Risks Analysis of a Large North American Population-Based Cohort
F. Abdollah, M. Sun, J. Schmitges, Z. Tian, C. Jeldres, A. Briganti, L. Shariat, P. Perrotte, F. Montorsi, P. Karakiewicz
European Urology 2011;60:920–930

2013

Prospective Assessment of Prostate Cancer Aggressiveness Using 3-T Diffusion-Weighted Magnetic Resonance Imaging–Guided Biopsies Versus a Systematic 10-Core Transrectal Ultrasound Prostate Biopsy Cohort
T. Hambrock, C. Hoeks, C. Hulsbergen-van de Kaa, T. Scheenen, J. Fütterer, S. Bouwense, I. van Oort, F. Schröder, H. Huisman, J. Barentsz
European Urology 2012;61:177–184

&

Immunocytology Is a Strong Predictor of Bladder Cancer Presence in Patients With Painless Hematuria: A Multicentre Study
E.K. Cha, L.-A. Tirsar, C. Schwentner, P.J. Christos, C. Mian, J. Hennenlotter, T. Martini, A. Stenzl, A. Pycha, S.F. Shariat, B.J. Schmitz-Dräger
European Urology 2012;61:185–192

2014

Prostate-specific Antigen (PSA) Testing Is Prevalent and Increasing in Stockholm County, Sweden, Despite No Recommendations for PSA Screening: Results from a Population-based Study, 2003–2011
T. Nordström, M. Aly, M.S. Clements, C.E. Weibull, J. Adolfsson, H. Grönberg
European Urology 2013;63:419–425

&

Metformin and Prostate Cancer: Reduced Development of Castration-resistant Disease and Prostate Cancer Mortality
D.E. Spratt, C. Zhang, Z.S. Zumsteg, X. Pei, Z. Zhang, M.J. Zelefsky
European Urology 2013;63:709–716

2015

Propensity-Matched Comparison of Morbidity and Costs of Open and Robot-Assisted Radical Cystectomies: A Contemporary Population-Based Analysis in the United States
J.J. Leow, S.W. Reese, W. Jiang, S.R. Lipsitz, J. Bellmunt, Q.-D. Trinh, B.I. Chung, A.S. Kibel, Steven L. Chang
European Urology 2014;66:569–576

&

Survival Outcome and Treatment Response of Patients with Late Relapse from Renal Cell Carcinoma in the

EUROPEAN UROLOGY

The Platinum Hall of Fame

Era of Targeted Therapy
N. Kroeger, T.K. Choueiri, J.-L. Lee, G.A. Bjarnason, J.J. Knox, M.J. MacKenzie, L. Wood, S. Srinivas, U.N. Vaishamayan, S.-Y. Rha, S.K. Pal, T. Yuasa, F. Donskov, N. Agarwal, M.-H. Tan, A. Bamias, C.K. Kollmannsberger, S.A. North, B.I. Rini, D.Y.C. Heng
European Urology 2014;65:1086–1092

2016

Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients
A.A. Azad, B.J. Eigl, R.N. Murray, C. Kollmannsberger, K.N. Chi
European Urology 2015;67:23–29
&
Preoperative Prostate-specific Antigen Isoform p2PSA and Its Derivatives, %p2PSA and Prostate Health Index, Predict Pathologic Outcomes in Patients Undergoing Radical Prostatectomy for Prostate Cancer: Results from a Multicentric European Prospective Study
N. Fossati, N.M. Buffi, A. Haese, C. Stephan, A. Larcher, T. McNicholas, A. de la Taille, M. Freschi, G. Lughezzani, A. Abrate, V. Bini, J. Palou Redorta, M. Graefen, G. Guazzoni, M. Lazzeri
European Urology 2015;68:132–138

2017

Renal Cell Carcinoma Programmed Death-ligand 1, a New Direct Target of Hypoxia-inducible Factor-2 Alpha, is Regulated by von Hippel–Lindau Gene Mutation Status
Y. Messai, S. Gad, M.Z. Noman, G. Le Teuff, S. Couve, B. Janji, S.F. Kammerer, N. Rioux-Leclerc, M. Hasmim, S. Ferlicot, V. Baud, A. Mejean, D.R. Mole, S. Richard, A.M.M. Eggermont, L. Albiges, F. Mami-Chouaib, B. Escudier, S. Chouaib
European Urology 2016;70:623–632
&
Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non–Muscle-invasive Bladder Cancer
T.J.H. Arends, O. Nativ, M. Maffezzini, O. de Cobelli, G. Canepa, F. Verweij, B. Moskovitz, A.G. van der Heijden, J.A. Witjes
European Urology 2016;69:1046–1052

2018

Ex Vivo Model of Human Penile Transplantation and Rejection: Implications for Erectile Tissue Physiology
N.A. Sopko, H. Matsui, D.M. Lough, D. Miller, K. Harris, M. Kates, X. Liu, K. Billups, R. Redett, A.L. Burnett, G. Brandacher, T.J. Bivalacqua
European Urology 2017;71:584–93
&
Racial Variation in Patient-Reported Outcomes Following Treatment for Localized Prostate Cancer: Results from the CEASAR Study
M.D. Tyson, J. Alvarez, T. Koyama, K.E. Hoffman, M.J. Resnick, X.-C. Wu, M.R. Cooperberg, M. Goodman, S. Greenfield, A.S. Hamilton, M. Hashibe, L.E. Paddock, A. Stroup, V.W. Chen, D.F. Penson, D.A. Barocas
European Urology 2017;72:307–14

2019

Prospective Implementation of Enhanced Recovery After Surgery Protocols to Radical Cystectomy
K.H. Pang, R. Groves, S. Venugopal, A.P. Noon, J.W.F. Catto
European Urology, Vol. 73, Issue 3, p363–371
&
Substitution Urethroplasty with Closure Versus Nonclosure of the Buccal Mucosa Graft Harvest Site: A Randomized Controlled Trial with a Detailed Analysis of Oral Pain and Morbidity
A. Soave, R. Dahlem, H.O. Pinnschmidt, M. Rink, J. Langetepe, O. Engel, L.A. Kluth, B. Loechelt, P. Reiss, S.A. Ahyai, M. Fisch
European Urology, Vol. 73, Issue 6, p910–922

2020

Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators
Arnout R. Alberts, Monique J. Roobol, Jan F.M. Verbeek, Ivo G. Schoots, Peter K. Chiu, Daniël F. Osses, Jasper D. Tijsterman, Harrie P. Beerlage, Christophe K. Mannaerts, Lars Schimmöller, Peter Albers, Christian Arsov
European Urology, Vol 75, Issue 2, p310–318
&
Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy
Elise De Bleser, Barbara Alicja Jereczek-Fossab, David Pasquierd, Thomas Zillif,, Nicholas Van Ash, Shankar Siva, Andrei Fodor, Piet Dirixl, Alfonso Gomez-Iturriaga, Fabio Trippa, Beatrice Dettip Gianluca Ingrosso, Luca Triggiani, Alessio Bruni, Filippo Along, Dries Reynders, Gert De Meerleer, Alessia Surgo, Kaoutar Loukili, Raymond Miralbellf, Pedro Silvah, Sarat Chander, Nadia Gisella Di Muzio, Ernesto Maranzano, Giulio Francolini, Andrea Lancia, Alison Treeh,i, Chiara Lucrezia Deantoni, Elisabetta Ponti, Giulia Marvaso, Els Goetghebeur, Piet Ost
European Urology, Vol 76, Issue 6, p732–739

Best Paper in Robotic Surgery

2016

Pilot Validation Study of the European Association of Urology Robotic Training Curriculum
A. Volpe, K. Ahmed, P. Dasgupta, V. Ficarra, G. Novara, H. van der Poel, A. Mottrie
European Urology 2015;68:292–299

2017

Measuring to Improve: Peer and Crowd-sourced

Assessments of Technical Skill with Robot-assisted Radical Prostatectomy
K.R. Ghani, D.C. Miller, S. Linsell, A. Brachulis, B. Lane, R. Sarle, D. Dalela, M. Menon, B. Comstock, T.S. Lendvay, J. Montie, J.O. Peabody, for the Michigan Urological Surgery Improvement Collaborative
European Urology 2016;69:547–550

2018

Multispectral Fluorescence Imaging During Robot-assisted Laparoscopic Sentinel Node Biopsy: A First Step Towards a Fluorescence-based Anatomic Roadmap
N.S. van den Berg, T. Buckle, G.H. KleinJan, H.G. van der Poel, F.W.B. van Leeuwen
European Urology 2017;72:110–17

2019

Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes
B.H. Bochner, G. Dalbagni, K.H. Marzouk, D.D. Sjoberg, J. Lee, S.M. Donat, J.A. Coleman, A. Vickers, H.W. Herr, V.P. Laudone
European Urology, Vol. 74, Issue 4, p465–471

2020

Robot-assisted AMS-800 Artificial Urinary Sphincter Bladder Neck Implantation in Female Patients with Stress Urinary Incontinence
Benoit Peyronnet, Gregoire Capon, Olivier Belas, Andrea Manunta, Clement Allenet, Juliette Hascoet, Jehanne Calves, Michel Belas, Pierre Callerot, Gregoire Robert, Aurelien Descazeaud, Georges Fournier
European Urology, Vol 75, Issue 1, p169–175

Platinum Award Winners 2009
1. Fritz Schröder
2. Urs Studer

Platinum Award Winners 2010
1. Christopher Chapple
2. Oliver Hakenberg
3. Rodolfo Montironi

Platinum Award Winners 2011
1. Guido Dalbagni
2. Monique J. Roobol

Platinum Award Winners 2012
1. Anders Bjartell
2. Markus Graefen
3. Mani Menon
4. Christian Stief
5. Tullio Sulser
6. Alexandre Zlotta

Platinum Award Winners 2013
1. Per-Anders Abrahamsson
2. Walter Artibani
3. Jacqueline Roelofswaard
4. Maurice Schlief
5. Claude Schulman
6. Pierre Teillac
7. Manfred Wirth
8. Hendrik van Poppel

Platinum Award Winners 2014
1. Inderbir Gill
2. Richard Sylvester
3. Henk van der Poel

Platinum Award Winners 2015
1. Stephen Freedland
2. Axel Heidenreich
3. Francesco Montorsi
4. Keith Parsons

Platinum Award Winners 2016
1. Matthew Gettman
2. George Thalmann

Platinum Award Winners 2017
1. Peter Albertsen
2. Axel Bex
3. James N'Dow
4. Daniel Sjoberg

Platinum Award Winners 2018
1. Peter Black
2. Christopher Evans
3. Joan Palou-Redorta
4. Monique Roobol
5. Shahrokh Shariat

Platinum Award Winners 2019
1. Stephen Boorjian
2. Fiona Burkhard
3. Pierre Karakiewicz
4. Luis Martinez-Piñeiro
5. Peter Mulders
6. Maria Ribal

Platinum Award Winners 2020
1. Prokar Dasgupta
2. Karim Fizazi
3. Silke Gillessen
4. Caroline Moore
5. Declan Murphy
6. Karin Plass

2007 Reviewers of the Month
January: Massimo Maffezzini (Italy)
February: Hiten R. H. Patel (UK)
March: Pierre Karakiewicz (Canada)
April: Christian Gratzke (Germany)

The Platinum Hall of Fame

May: Fred Witjes (The Netherlands)
June: Ziya Kirkali (Turkey)
July: Bertrand Guillonneau (USA)
August: Chris Chapple (UK)
September: Axel Heidenreich (Germany)
October: Jean-Jacques Patard (France)
November: Oliver Reich (Germany)

Reviewer of the Year 2007
Vincenzo Ficarra (Italy)

2008 Reviewers of the Month
January: Shahrokh Shariat (USA)
February: Alberto Briganti (Italy)
March: Alexander Bachmann (Switzerland)
April: Scott Eggener (USA)
May: Roger Dmochowski (USA)
June: Felix K.-H. Chun (Germany)
July: Giacomo Novara (Italy)
August: Michael Blute (USA)
September: Patrick Bastian (Germany)
October: Rafael Badalyan (Armenia)
November: Henk van der Poel (The Netherlands)

Reviewer of the Year 2008
Pierre Karakiewicz (Canada)

2009 Reviewers of the Month
January: Matthew Gettman (USA)
February: Oliver Hakenberg (Germany)
March: Riccardo Autorino (Italy)
April: Urs Studer (Switzerland)
May: Fritz Schröder (The Netherlands)
June: Petrisor Geavlete (Romania)
July: Clare Fowler (UK)
August: Francisco Cruz (Portugal)
September: John Denstedt (Canada)
October: Jacques Irani (France)
November: Apostolos Apostolidis (Greece)

Reviewer of the Year 2009
Henk van der Poel (The Netherlands)

2010 Reviewers of the Month
January: Ricarda Bauer (Germany)
February: Declan Murphy (Australia)
March: Harry Herr (USA)
April: Marko Babjuk (Czech Republic)
May: Umberto Capitanio (Italy)
June: Stephen Freedland (USA)
July: Richard Sylvester (Belgium)
August: Rufus Cartwright (UK)
September: Jens Rassweiler (Germany)
October: Mike Kattan (USA)
November: George Thalmann (Switzerland)

Reviewers of the Year 2010
Michael Kattan (USA)
Matthew Gettman (USA)
Giacomo Novara (Italy)

2011 Reviewers of the Month
January: Ofer Yossepowitch (Israel)
February: Theo de Reijke (The Netherlands)
March: Evangelos Liatsikos (Greece)
April: Christopher Eden (UK)
May: Ofer Gofrit (Israel)
June: James Catto (UK)
July: R. Houston Thompson (USA)
August: Karim Bensalah (France)
September: Gianluca Giannarini (Italy)
October: Mesut Remzi (Austria)
November: Peter Albertsen (USA)

Reviewer of the Year 2011
Alexander Bachmann (Switzerland)

2012 Reviewers of the Month
January: Francesco Greco (Germany)
February: Stephen Boorjian (USA)
March: Jean-Nicolas Cornu (France)
April: Mark Emberton (UK)
May: Firas Abdollah (Italy)
June: Stephan Madersbacher (Austria)
July: Michael Rink (Germany)
August: Rik Bryan (UK)
September: Sabine Brookman-May (Germany)
October: Nicolas Mottet (France)
November: Hendrik Isbarn (Germany)

Reviewers of the Year 2012
Peter Albertsen (USA)
Jean-Nicolas Cornu (France)
Gianluca Giannarini (Switzerland)

2013 Reviewers of the Month
January: Massimo Lazzeri (Italy)
February: Guillaume Ploussard (France)
March: Derya Tilki (Germany)
April: Giuseppe Simone (Italy)
May: Evanguelos Xylinas (USA)
June: Joseph Chin (Canada)
July: Rodolfo Montironi (Italy)
August: Matthew Galsky (USA)
September: Hashim Ahmed (UK)
October: Peter Black (Canada)
November: Tobias Klatte (Germany)

Reviewers of the Year 2013
Francesco Greco (Germany)
Stephen Boorjian (USA)
Matthew Galsky (USA)

2014 Reviewers of the Month
January: Morgan Rouprêt (France)
February: Malte Rieken (Switzerland)
March: Jochen Walz (France)
April: Noburo Hara (Japan)
May: Aidan Noon (UK)
June: Stacy Loeb (USA)

The Platinum Hall of Fame

July: Dan Sjoberg (USA)
August: Cosimo De Nunzio (Italy)
September: Michael Abern (USA)
October: Fumitaka Koga (Japan)
November: Christopher Barbieri (USA)

Reviewers of the Year 2014
Noboru Hara (Japan)
Aidan Noon (UK)
Christopher Barbieri (USA)

2015 Reviewers of the Month
January: Bertram Yuh (USA)
February: Francesco Porpiglia (Italy)
March: Henry Woo (Australia)
April: Umberto Anceschi (Italy)
May: Kazutaka Saito (Japan)
June: Alessandra Mosca (Italy)
July: Giorgio Gandaglia (Italy)
August: Sarah Psutka (USA)
September: Daniel Moreira (USA)
October: Boris Gershman (USA)
November: Roderick van den Bergh (The Netherlands)

Reviewers of the Year 2015
Giorgio Gandaglia (Italy)
Joseph Chin (Canada)
Boris Gershman (USA)

2016 Reviewers of the Month
January: Paolo Verze (Italy)
February: Liam Bourke (UK)
March: Brant Inman (USA)
April: Maurizio Serati (Italy)
May: William Parker (USA)
June: Homayoun Zargar (Australia)
July: Ola Bratt (UK)
August: Riccardo Bartoletti (Italy)
September: Zachary Klaassen (Canada)
October: Francesco Sanguedolce (Italy)
November: Antonio Galfano (Italy)

Reviewers of the Year 2016
Ola Bratt (Sweden)
Riccardo Bartoletti (Italy)
Zachary Klassen (Canada)

2017 Reviewers of the Month
January: Steeve Doizi (France)
February: Kazuto Ito (Japan)
March: Harras Zaid (USA)
April: Alberto Bossi (France)
May: Joshua Meeks (USA)
June: Zoran Culig (Austria)
July: Nicola Fossati (Italy)
August: Alexander Kutikov (USA)
September: Melissa Assel (USA)
October: Maximilien Gilles-André Baron (France)
November: Bimal Bhindi (Canada)

Reviewers of the Year 2017
Alexander Kutikov (USA)
Melissa Assel (USA)
Nicola Fossati (Italy)
Kazuto Ito (Japan)

2018 Reviewers of the Month
January: Andrea Necchi (USA)
February: Christopher Wallis (Canada)
March: Ross Mason (Canada)
April: Joseph Clark (USA)
May: Giorgio Russo (Italy)
June: Benoit Peyronnet (France)
July: Timothy Lyon (USA)
August: Ardalan Ahmad (Canada)
September: Alastair Lamb (UK)
October: Paul Boutros (Canada)
November: Paras Shah (USA)

Reviewers of the Year 2018
Andrea Necchi (USA)
Christopher Wallis (Canada)
Alastair Lamb (UK)

2019 Reviewers of the Month
January: Keith Lawson (Canada)
February: Alessandro Antonelli (Italy)
March: Christopher Filson (USA)
April: Scott Eggener (USA)
May: Sumanta Pal (USA)
June: Panagiotis Kallidonis (Greece)
July: Adam Weiner (USA)
August: Stephen Williams (USA)
September: Daniel Spratt (USA)
October: Jacob Patterson (UK)
November: Ryan Hutchinson (USA)

Reviewers of the Year 2019
Daniel Spratt (USA)
Jacob Patterson (UK)
Stephen Williams (USA)

2020 Reviewers of the Month
January: Mikkel Fode (DK)
February: Marco Borghesi (Italy)
March: Fumitaka Koga (JP)
April: Camilio Porta (Italy)
May: Jeffery Tosoian (USA)
June: Douglas Cheung (CAN)
July: Xavier Deffieux (France)
August: Yair Lotan (USA)
September: Daniel Geynisman (USA)
October: Andrea Cocci (Italy)

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Focus on the Quality of Prostate Multiparametric Magnetic Resonance Imaging: Synopsis of the ESUR/ESUI Recommendations on Quality Assessment and Interpretation of Images and Radiologists' Training

Maarten de Rooij[a], *Bas Israël*[a], *Tristan Barrett*[b], *Francesco Giganti*[c,d], *Anwar R. Padhani*[e], *Valeria Panebianco*[f], *Jonathan Richenberg*[g], *Georg Salomon*[h], *Ivo G. Schoots*[i,j], *Geert Villeirs*[k], *Jochen Walz*[l], *Jelle O. Barentsz*[a,*]

[a] *Department of Radiology, Nuclear Medicine, and Anatomy, Radboudumc, Nijmegen, The Netherlands;* [b] *Department of Radiology, CamPARI Prostate Cancer Group, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK;* [c] *Department of Radiology, University College London Hospital NHS Foundation Trust, London, UK;* [d] *Division of Surgery & Interventional Science, University College London, London, UK;* [e] *Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, UK;* [f] *Department of Radiological Sciences, Oncology and Pathology, Sapienza University of Rome, Rome, Italy;* [g] *Department of Imaging, Brighton and Sussex University Hospital NHS Trust, Brighton, UK;* [h] *Martini Clinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [i] *Department of Radiology & Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands;* [j] *Department of Radiology, Netherlands Cancer Institute, Amsterdam, The Netherlands;* [k] *Department of Radiology, Ghent University Hospital, Ghent, Belgium;* [l] *Department of Urology, Institute Paoli-Calmettes Cancer Center, Marseille, France*

Introduction

Multiparametric magnetic resonance imaging (mpMRI) has an established upfront role in the diagnostic pathway for men with a clinical suspicion of prostate cancer [1,2]. The patient benefits from prebiopsy use of prostate MRI to decide on subsequent MRI-guided biopsy (MRI pathway) compared to a systematic transrectal ultrasound–guided biopsy approach (SB) in three ways. The MRI pathway can reduce the number of unnecessary biopsies, minimise overdiagnosis of low-grade (grade group [GG] $\geq$1) cancers with noninferiority for detecting clinically significant (GG $\geq$2) cancers [3], and improve risk stratification of patients by facilitating targeted biopsies [4].

Incorporation of prostate MRI in the diagnostic pathway will lead to an increase in demand for high-quality mpMRI. In Europe and the USA, this is predicted to equate annually to approximately two million additional prostate MRI scans. In clinical practice, there is considerable variation in acquisition parameters and image quality for prostate MRI [5]. It is of paramount importance that all examinations and subsequent reports are of the highest quality for a test that is central to triage. Poor quality will result in both unnecessary biopsies and missed diagnosis of clinically significant cancer. Paradoxically, there is a lack of agreed—let alone stringent—standards for acquisition that are applicable to all radiologists who independently read prostate MRI scans. To ensure the availability of high-quality prostate MRI scans between centres and radiologists at this time of expansion, the Prostate MRI Quality Subcommittees of the European Society of Urogenital Radiology (ESUR) and the European Association of Urology Section of Urologic Imaging (ESUI) formulated consensus-based criteria for prostate MRI acquisition, reporting, and training [6].

Synopsis of quality consensus statements

The ESUR and ESUI consensus paper comprises a structured and systematic summary of the opinions of recognised experts in diagnostic prostate MRI on quality measures that are not adequately addressed by existing literature. For this purpose, a modified Delphi-method was used with a panel of 44 expert prostate radiologists and urologists specialised in prostate imaging. The panellists completed two rounds of

* Corresponding author: Department of Radiology, Radboudumc, Nijmegen, P.O. Box 9101, The Netherlands.
E-mail address: jelle.barentsz@radboudumc.nl (J.O. Barentsz).

https://doi.org/10.1016/j.eururo.2020.06.023

Table 1 – Consensus-based recommendations on image quality assessment, evaluation of interpretation performance, and reader experience with prostate mpMRI [6]

Image quality	Interpretation performance	Reader experience
Checking and reporting on image quality should be performed	To evaluate interpretation performance, radiologists should use self-performance tests	Before interpreting prostate mpMRI scans, radiologists should receive training
		Radiologists should undertake a combination of core theoretical prostate mpMRI courses and hands-on practice at workstations with supervised reporting
		Training should be certified
Visual image assessment by radiologists is adequate for determining diagnostic acceptability	Assessment of radiologists' performance should be performed using histopathology feedback and by comparison to expert reading	For good prostate mpMRI quality, assessment of technical quality measures should be in place
		A peer review of image quality should be organised
		Minimal technical requirements of PI-RADS v2 should be met
Image quality control should be performed at ≥6-mo intervals or in 5% of studies	To evaluate the radiologists' interpretation performance, external performance assessments should be done	PI-RADS should be used as the basis for assessments
		Prostate radiologists should be aware of alternative diagnostic methods
		Radiologists should participate in MDT meetings or attend MDT-type workshops
		The MDT must include MRI review with histology results
The radiology community should work on a standardised phantom for ADC measurements		The MDT must include urology, radiology, pathology, and medical and radiation oncology specialists
		Prostate radiologists should have knowledge on the added value of MRI and the consequences of false results
		Prostate radiologists should have roles in shared decision-making with respect to biopsy strategies

ADC = apparent diffusion coefficient; MDT = multidisciplinary team; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System.

a questionnaire comprising 55 items addressing three main topics: (1) assessments of image quality for prostate MRI; (2) requirements for radiologists interpreting and reporting prostate MRI; and (3) learning and experience prerequisites for independent reporting. Thirty-one of the 55 questions (56%) were rated for agreement on a 9-point scale, while the other 24 (44%) were multiple choice or open questions. The consensus-based recommendations formulated are summarised in Table 1.

Image quality assessment

The panellists agreed that commenting on image quality based on visual assessment by the reporting radiologist is mandatory in order to indicate the diagnostic power of the MRI study. For MRI radiographers this will provide feedback for quality improvement. For urologists, it will indicate the value of the particular MRI scan in their clinical management, that is, how reliably a GG ≥ 2 cancer can be ruled out or ruled in, or whether the scan should be repeated. A set of objective criteria for assessing image quality is not provided in the current consensus paper. The ESUR/ESUI Prostate MRI Quality Subcommittees hope to develop a consensus-based scoring system that will require prospective validation to fill this gap.

Prerequisites for interpretation and reporting for MRI readers

The panellists agreed that radiologists should monitor their individual diagnostic performance through (1) audit against histopathology feedback; (2) (self-)performance tests; and (3) comparison of their results against expert readers. In addition, benchmarking to peers' performances should be undertaken.

Radiologists' learning and reporting expertise

The members of the expert panel suggest mandatory use of the Prostate Imaging-Reporting and Data System (PI-RADS) standardised reporting system and the introduction of distinct quality criteria levels for radiologists who want to become independent prostate MRI readers or expert readers. The criteria are based on the number of cases read, cases per year, (self-)performance tests, and percentage agreement with expert training centres (Table 2). Before reading prostate MRI scans, radiologists must attend a combination of theoretical and hands-on courses, followed

Table 2 – Consensus-based criteria for basic versus expert radiologists [6]

Criterion	Basic	Expert
Minimum number of supervised cases before independent reporting	100	N/A
Minimum number of cases read	400	1000
Minimum number of cases per year	150	200 [a]
Examination interval (yr)	1	4
Agreement in double reads with expert centre (%)	80	≥90

N/A = not applicable.
[a] No panel majority; the most frequent answer was 200 cases/yr (18/44 of panellists, 41%); the second most frequent answer was ≥500 cases/yr (14/44 of panellists, 32%).

by supervised education. Participation in multidisciplinary team (MDT) meetings is compulsory. In MDTs, urologists, pathologists, and radiologists are advised to critically review PI-RADS scores versus the histopathology of biopsy cores or whole-mount radical prostatectomy specimens in order to reduce overdiagnosis and underdiagnosis of GG $\geq$ 2 cancers. Furthermore, radiologists should play an active role in the decision-making process on the need for MRI-targeted biopsies and the method by which they are carried out.

Conclusions

This consensus expert opinion report from ESUR and ESUI members builds on the standards set out in the PI-RADS documents. It provides guidance on prostate MRI acquisition and sets out metrics to gauge and to improve on the reporting expertise of clinicians involved in prostate cancer diagnosis. These criteria, which were derived using the Delphi method, are likely to serve as a starting point for certification of individual radiologists for performing unsupervised reading of prostate MRI scans and for accreditation of centres for their prostate MRI diagnostic pathway. The goal is a centre providing high-quality image acquisition, confident and reliable MRI reports, precise targeted biopsies, and accurate pathology assessment. More immediately, these criteria may help to focus the entire MDT on MRI quality and thus continuous development of radiological expertise and clinical-radiological dialogue.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Bjurlin MA, Carroll PR, Eggener S, et al. Update of the standard operating procedure on the use of multiparametric magnetic resonance imaging for the diagnosis, staging and management of prostate cancer. J Urol 2020;203:706–12.

[2] Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. Arnhem The Netherlands: European Association of Urology 2020.

[3] Drost FH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol 2020;77:78–94.

[4] Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917–28.

[5] Burn PR, Freeman SJ, Andreou A, Burns-Cox N, Persad R, Barrett T. A multicentre assessment of prostate MRI quality and compliance with UK and international standards. Clin Radiol 2019;74:894.e19–e.

[6] de Rooij M., Israel B., Tummers M., et al., ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. Eur Radiol. In press. 10.1007/s00330-020-06929-z.

EUROPEAN UROLOGY 78 (2020) 486–488

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

DNA Repair and Prostate Cancer: A Field Ripe for Harvest

Alan H. Bryce [a], *Oliver Sartor* [b,*], *Johann de Bono* [c,d]

[a] *Department of Oncology, Mayo Clinic, Scottsdale, AZ, USA;* [b] *Cancer Center, Tulane Medical School, New Orleans, LA, USA;* [c] *Experimental Cancer Medicine, Institute for Cancer Research, London, UK;* [d] *Royal Marsden Hospital, London, UK*

There was welcome news for prostate cancer patients with the recent data showing antitumor activity for four PARP inhibitors; two of these; (olaparib and rucaparib) are now approved by the US Food and Drug Administration (FDA) for men with metastatic castrate-resistant prostate cancer (mCRPC) with selected DNA repair defects (DRDs) [1,2]. Additional clinical trials are in progress for talazoparib, veliparib, and niraparib [3,4]; more progress can be anticipated in the near future.

Rucaparib was given accelerated approval for the treatment of mCRPC with deleterious *BRCA* alterations (germline and/or somatic) previously treated with both abiraterone/enzalutamide and docetaxel. Olaparib was approved for mCRPC progressing after enzalutamide and/or abiraterone with deleterious germline alterations in *BRCA1*/*BRCA2* or various somatic homologous recombination repair (HRR) defects. Olaparib was approved for those with somatic deleterious alterations in the *BRCA* genes and *ATM*, *BARD*, *BRIP*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. These PARP inhibitors represent the second precision medicine approach approved relevant to prostate cancer; the first was pembrolizumab for cancers with defective mismatch-repair or microsatellite instability (MSI high) [5]. The FDA approval of these PARP inhibitors and pembrolizumab now mandate genomic analysis of advanced prostate cancer.

While the *BRCA* genes are central to HRR, some of the other alterations prospectively studied in mCRPC PARP inhibitor trials are involved in DNA repair but not directly involved in HRR. Available evidence for antitumor activity against DRDs in mCRPC without *BRCA* alterations is potentially positive (Table 1) but quite limited for the relatively rare patients with alterations in *PALB2*, *BRIP1*, *RAD51B*, *RAD54L*, and *FANCA*, and quite modest for DRD alterations in *ATM*. Data supporting the antitumor activity of PARP inhibitors are unclear for patients with deleterious alterations in *BARD*, *CHEK1*, *CHEK2*, *FANCL*, *RAD51C*, and *RAD51D*.

ATM senses DNA damage and activates DNA repair, and is thus only indirectly involved in HRR. Responses to PARP inhibitors in mCRPC with deleterious *ATM* alterations have been observed but the PFS data in PROfound were not distinct from the control group [2]. However, there were significant differences between the pre- and post-taxane cohorts, with the latter appearing to experience more benefit. Radiographic response rates across multiple phase 2 trials have ranged from 10.5% in TRITON2 to 8.3% in TOPARP-B and 7.1% in TALAPRO-1 [1,3,6].

CDK12 regulates the expression of multiple DNA repair genes and is key to genomic stability, but is not directly involved in HRR. Data to support PARP inhibitor antitumor activity for those with altered *CDK12* are arguably limited, but preliminary data suggest that pembrolizumab may have antitumor activity for this subset [7].

Critically important challenges to these analyses include data generation and analyses for putative predictive biomarkers; these represent a clear deficiency in the current state of the art, with difficulties in the following:

- Acquiring genomic sequencing from small paraffin-embedded, formalin-fixed biopsies;
- Understanding that these alterations may emerge with treatment, and may only be present in mCRPC biopsies; and
- Interpreting genomic data to identify sensitizing alterations.

Importantly, approximately 30% of tumor tissue blocks submitted for testing in the olaparib PROfound trial failed quality control testing, with no genomic testing data

* Corresponding author at: Cancer Center, Tulane Medical School, 1430 Tulane Avenue, New Orleans, LA 70112, USA. Tel. +1 5043557970.
E-mail address: osartor@tulane.edu (O. Sartor).

https://doi.org/10.1016/j.eururo.2020.06.020

Table 1 – Genes involved in HRR, trial results, and recommendations for clinical use of PARP inhibitors.

Gene	Role in HRR	Clinical benefit [2–4,7,8]	Evidence-based assessment
BRCA2 (FANCD1)	Binds directly to *RAD51* to facilitate its recruitment to sites of DNA double strand breaks (DSB). Leads to the recruitment of *BRCA1* and CtIP proteins to sites of DNA DSB.	PROfound: HR 0.21 (95% CI 0.13–0.32) TRITON 2: *n* = 98; 25/57 (44%), 51/98 (52%) [a] TOPARP-B: *n* = 30; RR 11/21 (52%), PSA_{50} 23/30 (77%), CTC = 17/22 (77%) [a] TALAPRO-1: *n* = 40; RR 22/32 (68.8%), PSA_{50} 29/40 (73%) GALAHAD: *n* = 23; 5/13 (39%), PSA_{50} 13/23 (57%), CTC 11/23 (48%) [a]	Clear benefit from PARP inhibitors
BRCA1	Required for initiation of precise end-joining repair via interaction with *Ku80* at DSB sites and promotes HRR via dephosphorylation of *53BP1*	PROfound: HR 0.41 (05% CI 0.13–1.39) TRITON 2: *n* = 98; 25/57 (43.9%), 51/98 (52%) [a] TOPARP-B: *n* = 30; RR 11/21 (52%), PSA_{50} 23/30 (77%), CTC 17/22 (77%) [a] TALAPRO-1: *n* = 5; RR 2/4 (50%), PSA_{50} 2/5 (40%) GALAHAD: *n* = 23; 5/13 (39%), PSA_{50} 13/23 (57%), CTC 11/23 (48%) [a]	Clear benefit from PARP inhibitors
ATM	Controls cell-cycle checkpoint signaling pathways that are needed to initiate HRD in the presence of DNA damage; however, *ATM* null cells remain HRR proficient, suggesting that *ATM* loss is not a HRD aberration	PROfound: HR 1.04 (95% CI 0.61–1.87) TRITON 2: *n* = 49; RR 2/19 (11%), PSA_{50} 2/49 (4%) TOPARP-B: *n* = 19; RR 1/12 (8 %), PSA_{50} 1/19 (5%), CTC 5/10 (50%) TALAPRO-1: *n* = 16; RR 2/14 (14%), PSA_{50} 4/16 (25%)	Modest antitumor activity; further study needed; trial participation preferred; ATR inhibitors, and ATR combinations perhaps with PARP inhibitors, merit clinical evaluation
BARD1	Controls cell cycle in the presence of DNA damage via interaction with *BRCA1*	No data available	No evidence for PARP inhibitor use; trial participation preferred
BRIP1 (FANCJ)	Associates with the *BRCA1* complex at DSB sites	TRITON 2: *n* = 2; RR 1/2 (50%); PSA_{50} 1/2 (50%)	Limited data demonstrating potential activity; further study needed; trial participation preferred
CDK12	Phosphorylates RNA polymerase II and selectively affects the expression of genes involved in DNA damage response, thus indirectly impacting HRD	PROfound: HR 0.74 (95% CI 0.44–1.31) TRITON 2: *n* = 15; RR 0/10 (0%), PSA_{50} 1/15 (7%) TOPARP-B: *n* = 20; RR 0/18 (0%), PSA_{50} 0/20 (0%), CTC 5/12 (42%)	At best, modest antitumor activity; further data needed; trial participation preferred; immune checkpoint drugs targeting PD-1/PD-L1 should be considered
CHEK2	Cell-cycle checkpoint inhibitor that activates DNA repair and apoptosis in the presence of DSBs via phosphorylation of *BRCA1* and *BRCA2* (repair) and of *TP53* (apoptosis)	PROfound: HR 0.87 (95% CI 0.23–4.13) TRITON 2: *n* = 12; 1/9 (11%), PSA_{50} 2/12 (17%)	Little evidence for antitumor activity; trial participation preferred; role of ATR inhibitors and their combinations merits exploration in this subset
FANCA	Part of the Fanconi anemia core complex that initiates DNA repair by attracting HRD proteins to the area of DNA damage; interacts directly with *BRCA1*	TRITON 2: *n* = 4; RR 1/4 (25%), PSA_{50} 1/4 (25%)	Limited data demonstrating potential activity; further study needed; trial participation preferred
NBN (NIBRIN)	P95 protein is part of the *RAD50*/*MRE*/*NBS1* complex involved in DNA repair	TRITON 2: *n* = 4; RR 0/4 (0%), PSA_{50} 0/4 (0%)	No antitumor activity seen in limited data; further study needed; trial participation preferred
PALB2	Recruits *RAD51* and *BRCA2* to sites of DNA breaks and serves as the molecular scaffold for the *BRCA2-RAD51* complex in HRR	PROfound: *n* = 7; RR 2/6 (33%), 4/6 (67%) TRITON 2: *n* = 2; RR 1/2 (50%), PSA_{50} 2/2 (100%) TOPARP-B: *n* = 7; RR 2/6 (33%), PSA_{50} 4/6 (67%), CTC 0/2 (0%) TALAPRO-1: *n* = 3; RR 1/2 (50%), PSA_{50} 2/3 (66.7%)	Consistent antitumor activity in limited data sets; clinical use of PARP inhibitors is justifiable, but further study or meta-analysis preferred; trial participation preferred
RAD51	Binds to sites of DNA breaks and encases the DNA in a protein sheath to initiate HRR; activity directly regulated by *BRCA2*	TRITON 2: *n* = 1; RR 0/1 (0%), PSA_{50} 0/1 (0%)	No antitumor activity seen in limited data; further study needed; trial participation preferred
RAD51B	Forms a dimer with *RAD51C* to bind to DSB sites	TRITON 2: *n* = 1; RR 1/1 (100%), PSA_{50} 1/1 (100%)	Limited data demonstrating potential antitumor activity; further study needed; trial participation preferred
RAD51D	Forms a protein complex with *RAD 51L1*, *RAD 51L2*, and *XRCC2* to catalyze homologous pairing between ssDNA and dsDNA	No data available	No evidence for PARP inhibitor use; trial participation preferred
RAD54L	Involved in the recombinatorial DNA repair pathway (*RAD52*); may dissociate *RAD51* from dsDNA	PROfound: HR 0.33 (95% CI 0.05–2.54) TRITON 2: *n* = 1; RR 0/1 (0%), PSA_{50} 0/1 (0%)	Limited data with potential antitumor activity; further study needed; trial participation preferred
PPP2R2A	Limited data; purported role as a tumor suppressor	PROfound: HR 6.61 (95% CI 1.41–46.41)	No antitumor activity seen in limited data; further study needed; trial participation preferred

CI = confidence interval; CTC = conversion of circulating tumor cell count; DSBs = double-strand breaks; dsDNA = double-stranded DNA; HR = hazard ratio for progression-free survival; HRR = homologous recombination repair; PSA_{50} = 50% reduction in prostate-specific antigen from baseline; RR = RECIST response rate; ssDNA = single-stranded DNA.

[a] Combined *BRCA1/2* results.

generated; this is clearly an area in need of improvement. Moreover, most of these tissues were archival biopsy or surgical specimens from the original prostate and not mCRPC tissue samples. While HRR alterations are often early events, evolution of HRR alterations in lethal subclones also occurs and studies of archival tissues may therefore provide inaccurate predictive biomarker data. Contemporaneous mCRPC assessment, however, remains challenging because of tissue accessibility, although the Triton study showed that liquid biopsies (eg, circulating tumor DNA) have high concordance with tissue biopsies.

Furthermore, biomarker studies conducted to date have not always distinguished between monoallelic and biallelic loss, and have failed to focus on the loss of protein function that creates the synthetic lethal interaction. Moreover, genomic alterations represent only one means of protein loss of function; promoter hypermethylation and microRNAs can also, for example, change protein expression without altering gene structure, and it is likely that in some tumors multiple alterations together lead to sensitization to PARP inhibition.

Overall, we envision that better assessment of tumor genomics will include contemporaneous sample analyses for biallelic deleterious alterations, with orthogonal functional assays detecting impaired DNA repair. Furthermore, analyses of disease evolution and subclone analyses are needed both to assess responsiveness to PARP inhibition and to monitor resistance. Positron emission tomography imaging of PARP activity as a biomarker is also an area of potential interest given the ability to carry out whole-body serial assessments. Much progress needs to occur at the intersection of biomarkers and clinical studies of PARP inhibition. There are also preclinical data suggesting that non-HRR gene loss may also be synthetically lethal with PARP inhibition, including loss of *RNASEH2B* at the *RB1* chromosome 13 locus [2]; additional studies are needed to evaluate this.

Finally, while PARP inhibition is clearly active as monotherapy, other agents that damage DNA may have antitumor activity against DRD mCRPC. Chemotherapy agents such as various platinum compounds, cyclophosphamide, and radiopharmaceuticals such as ^{223}Ra and ^{177}Lu PSMA-617 have been associated with clinical antitumor activity. Limited data comparing PARP inhibitors to other DNA-damaging agents are available, but more data are forthcoming. Multiple studies in prostate cancer combining PARP inhibitors with additional agents are under way, including a variety of DNA-damaging agents (^{223}radium, ^{177}Lu PSMA-617), immunomodulators (eg, pembrolizumab), and androgen axis blockers (abiraterone, enzalutamide). The rationale for these combinations in preclinical studies is clear but the current clinical data are immature. In addition, studies of novel agents targeting other DNA repair enzymes are of interest, including *ATR* inhibition which is of special interest for *ATM* altered mCRPC as well as tumors with *RNASH2B/RB1* loss. Taken together, research studies of DNA repair defects in prostate cancer and their targeting are likely to yield a rich harvest and improve patient care over the next decade.

Conflicts of interest: Alan H. Bryce has received consulting fees from Astellas and Bayer. Oliver Sartor has received consulting fees from Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion Pharmaceuticals, Janssen, Myovant, Myriad, Noria Therapeutics Inc., Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix Pharmaceuticals, and Theragnostics. Johann de Bono has received consulting fees and advisory board fees from Astellas Pharma, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Genentech, GlaxoSmithKline, Janssen Global Services, Menarini Silicon Biosystems, Merck, Merck Sharp & Dohme, Orion, Pfizer, Qiagen Sciences, Sanofi-Aventis U.S., Sierra Oncology, Taiho Pharmaceutical, and Vertex Pharmaceuticals, and has a holding in a patent (WO/2005/053662) on DNA damage repair inhibitors for treatment of cancer held by the Institute of Cancer Research and licensed to AstraZeneca, and a patent (US5604213) on 17-substituted steroids useful in cancer treatment held by the Institute of Cancer Research and licensed to Janssen Global Services.

References

[1] Abida W, Campbell D, Patnaik A, et al. Genomic characteristics associated with clinical activity of rucaparib in patients (pts) with BRCA1 or BRCA2 (BRCA)-mutated metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2020;38(6 Suppl):178.

[2] de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. New Engl J Med 2020;382:2091–102.

[3] de Bono JSD, Mehra N, Higano CS, et al. TALAPRO-1: phase II study of talazoparib (TALA) in patients (pts) with DNA damage repair alterations (DDRm) and metastatic castration-resistant prostate cancer (mCRPC) – updated interim analysis (IA). J Clin Oncol 2020;38 (15 Suppl):5566.

[4] Smith MR, Sandhu SK, Kelly WK, et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): preliminary results of GALAHAD. J Clin Oncol 2019;37(7 Suppl):202.

[5] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. New Engl J Med 2015;372:2509–20.

[6] Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2019;21:162–74.

[7] Abida W., Campbell D., Patnaik A., et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. Clin Cancer Res. In press. 10.1158/1078-0432.ccr-20-0394.

[8] Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:162–74.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Re-establishing the Role of Robot-assisted Radical Cystectomy After the 2020 EAU Muscle-invasive and Metastatic Bladder Cancer Guideline Panel Recommendations

Francesco Montorsi [a,], Marco Bandini [a], Alberto Briganti [a], Prokar Dasgupta [b], Andrea Gallina [a], Michele Gallucci [c], Inderbir S. Gill [d], Khurshid A. Guru [e], Ashok Hemal [f], Mani Menon [g], Marco Moschini [a,h], Declan G. Murphy [i], Dipen J. Parekh [j], Hiten D. Patel [k], Hiten R.H. Patel [l], Michael Stöckle [m], Ash K. Tewari [n], Carl J. Wijburg [o], Peter Wiklund [n,p], Timothy G. Wilson [q], Alexandre Mottrie [r,s], in collaboration with the EAU Robotic Urology Section Scientific Working Group*

[a] *Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy;* [b] *MRC Centre for Transplantation, King's College London, Department of Urology, Guy's Hospital, London, UK;* [c] *Department of Urology, Sapienza University, Rome, Italy;* [d] *Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [e] *Department of Urology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA;* [f] *Department of Urology, Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA;* [g] *Henry Ford Health System, Detroit, MI, USA;* [h] *Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland;* [i] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, East Melbourne, Australia;* [j] *Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA;* [k] *The James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [l] *Department of Urology, University Hospital of Northern Norway, Tromsø, Norway;* [m] *University of the Saarland, Homburg Saar, Germany;* [n] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [o] *Rijnstate Hospital, Arnhem, The Netherlands;* [p] *Department of Molecular Medicine and Surgery, Section of Urology, Karolinska Institutet, Stockholm, Sweden;* [q] *John Wayne Cancer Institute, Santa Monica, CA, USA;* [r] *Department of Urology, Onze Lieve Vrouw Hospital, Aalst, Belgium;* [s] *ORSI Academy, Melle, Belgium*

Every year, the European Association of Urology (EAU) guideline panels make huge efforts to provide updated guidelines for the urology community that are essential to the improvement of routine clinical practice [1].

We have read with great interest the 2020 updated version of the guidelines on muscle-invasive and metastatic bladder cancer (MIBC) [2] and we would like to commend the panel for their monumental work. This being said, we were surprised to note that the panel defined open radical cystectomy (ORC) as the best surgical approach for MIBC patients [2]. Robot-assisted radical cystectomy (RARC) was introduced into clinical practice more than 17 yr ago, when Menon and colleagues' pioneered the field and described the technique [3], 4 yr after the da Vinci Surgical System was approved by the US Food and Drug Administration [4].

Since then, there have been continuous efforts to examine the surgical safety, the oncological and functional efficacy, and the cost-effectiveness of RARC compared to the previous standard of care of ORC. Following the initial small, single-center case series [3,5], a large consortium was formed to prospectively enroll and monitor patients undergoing RARC in tertiary care centers [6–8]. Subsequently, updated data were published by this multi-institutional collaboration showing that RARC was safe and possibly advantageous in terms of in-hospital length of stay and perioperative transfusions. Along with these retrospective and nonrandomized data, five prospective randomized clinical trials (RCTs) [9–13] involving a total of 541 participants compared RARC and ORC in attempts to identify the technique of choice for radical cystectomy. Individual and pooled results [14,15] from these RCTs confirmed that RARC and ORC are similar in terms of oncological control (ie, time to recurrence), rates of positive margins, nodal yields, major complications (ie, Clavien-Dindo grades 3–5), and quality of

* Corresponding author. Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina 60, Milan 20132, Italy. Tel. +39 02 26437286, Fax: +39 02 26437298.
E-mail address: montorsi.francesco@hsr.it (F. Montorsi).

https://doi.org/10.1016/j.eururo.2020.06.035

life after surgery. An initial concern about aberrant local recurrence patterns and peritoneal carcinomatosis after RARC [16] has been rebutted [17] and conclusively refuted by these RCT data [14]; equally, this has just not been an issue in the worldwide RARC experience. Besides these similar findings, RARC probably results in lower blood loss and may lead to a shorter hospital stay and a lower rate of minor complications (Clavien grades 1 and 2) compared to ORC. Furthermore, preliminary data also suggest that the RARC approach is not negatively affected by neoadjuvant treatments, including both chemotherapy and immunotherapy [18–22]. Here, RARC showed similar rates of perioperative complications and noninferior surgical safety when compared to the open approach [23]. In addition, the feasibility of RARC was demonstrated in octogenarians and surgically complex patients [24,25]. Finally, from a surgical standpoint, RARC may reduce the learning curve, allowing faster training of experienced surgeons, who are claimed to be the main trigger for improving surgical safety and surgical outcomes [26–29]. Furthermore, RARC also seems to be favored from an ergonomic perspective for the urologist and the team members. Taking these points together and given the lack of clear superiority of one approach over the other, it should be concluded that RARC cannot be qualified as the standard of care for the surgical treatment of bladder cancer, but neither can the opposite be the case.

The robotic approach has gained in popularity, with patients increasingly requesting to be treated with RARC given its advantages such as the minimally invasive nature and shorter hospital stay and postoperative recovery. A recent study comparing trends in the use of RARC and ORC across tertiary-care teaching institutions in Europe and North America found that RARC has become the procedure more commonly performed among contemporary patients, with an increase from 29% in 2006–2008 to 54% in 2015–2018, while ORC decreased from 71% in 2006–2008 to 46% in 2015–2018 ($p < 0.001$) [30].

The pros and cons of a robotic versus an open approach have also been assessed for other urological malignances. Robot-assisted radical prostatectomy and robot-assisted partial nephrectomy have proved to be noninferior in terms of surgical safety with similar postoperative rates of complications compared their open counterparts. Only one RCT comparing open versus robotic radical prostatectomy was published [31], and a few nonrandomized studies compared robotic and open partial nephrectomy [32]. Nevertheless, neither the prostate cancer [33] nor the kidney cancer [34] EAU Guideline Panels tipped the balance towards one or other technique, leaving informed patients with the choice of their preferred approach, as long as the choice is made between surgeons with similar experience in the two techniques.

We respectfully suggest that the MIBC Guidelines Panel statements that ORC is the “current best practice” and that RARC is “feasible but still investigational” do not reflect the real-life scenario or the contemporary literature. Available level 1A evidence proves that RARC and ORC can both be offered to patients as there are no significant perioperative, postoperative, or long-term functional or oncological outcome differences, similar to the situation for prostate and kidney surgery. The evidence supporting RARC (five RCTs) is indeed much more robust than the evidence available for robotic radical prostatectomy (one RCT) or robotic partial nephrectomy (only retrospective evidence), yet nobody would argue about the contemporary role of robotic surgery in the latter two scenarios. We agree that RARC is still not performed in every center and is mainly centralized in tertiary care teaching institutions. This is mainly because RARC is an expensive procedure, primarily owing to the cost of the robot, which therefore is not available everywhere. In addition, radical cystectomy is a complex surgical procedure with high complication rates [22,23] regardless of the approach chosen (RARC vs ORC). As a consequence, radical cystectomy, whether ORC or RARC, should be performed only in high-volume centers where, as noted, a robotic platform is commonly available and used on a daily basis.

In conclusion, we believe that on the basis of the contemporary evidence and the worldwide trend towards increasing adoption of RARC, the MIBC Guidelines Panel should reconsider the recommendation suggesting ORC as the first choice for surgical management of bladder cancer. We believe that the surgeon’s understanding of the disease process, technical skills, and overall experience should be the main deciding factors when choosing between RARC and ORC.

Conflicts of interest: The authors have nothing to disclose.

References

[1] European Association of Urology. Guidelines. https://uroweb.org/guidelines/.
[2] Witjes J.A., Bruins H.M., Cathomas R., et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.03.055.
[3] Menon M, Hemal AK, Tewari A, et al. Nerve-sparing robot-assisted radical cystoprostatectomy and urinary diversion. BJU Int 2003;92:232–6.
[4] US Food and Drug Administration. www.fda.gov/home.
[5] Beecken W-D-D, Wolfram M, Engl T, et al. Robotic-assisted laparoscopic radical cystectomy and intra-abdominal formation of an orthotopic ileal neobladder. Eur Urol 2003;44:337–9.
[6] Raza SJ, Wilson T, Peabody JO, et al. Long-term oncologic outcomes following robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. Eur Urol 2015;68:721–8.
[7] Hussein AA, Elsayed AS, Aldhaam NA, et al. Ten-year oncologic outcomes following robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. J Urol 2019;202:927–35.
[8] Hussein A.A., Elsayed A.S., Aldhaam N.A., et al. A comparative propensity score-matched analysis of perioperative outcomes of intracorporeal vs extracorporeal urinary diversion after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. BJU Int. In press. https://doi.org/10.1111/bju.15083.
[9] Messer JC, Punnen S, Fitzgerald J, Svatek R, Parekh DJ. Health-related quality of life from a prospective randomised clinical trial of robot-

assisted laparoscopic vs open radical cystectomy. BJU Int 2014;114:896–902.
[10] Bochner BH, Dalbagni G, Marzouk KH, et al. Randomized trial comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: oncologic outcomes. Eur Urol 2018;74:465–71.
[11] Khan MS, Omar K, Ahmed K, et al. Long-term oncological outcomes from an early phase randomised controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy (CORAL). Eur Urol 2020;77:110–8.
[12] Nix J, Smith A, Kurpad R, Nielsen ME, Wallen EM, Pruthi RS. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. Eur Urol 2010;57:196–201.
[13] Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet 2018;391:2525–36.
[14] Rai BP, Bondad J, Vasdev N, et al. Robotic versus open radical cystectomy for bladder cancer in adults. Cochrane Database Syst Rev 2019;2019:CD011903.
[15] Satkunasivam R, Tallman CT, Taylor JM, Miles BJ, Klaassen Z, Wallis CJD. Robot-assisted radical cystectomy versus open radical cystectomy: a meta-analysis of oncologic, perioperative, and complication-related outcomes. Eur Urol Oncol 2019;2:443–7.
[16] Nguyen DP, Al Hussein Al Awamlh B, Wu X, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. Eur Urol 2015;68:399–405.
[17] Pourmalek F, Abdi H, Black PC, Re: Daniel P. Nguyen, Bashir Al Hussein Al Awamlh, Xian Wu, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. Eur Urol 2015;68:399–405, Eur Urol 2016;69:e35.
[18] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
[19] Necchi A, Raggi D, Gallina A, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. Eur Urol 2020;77:439–46.
[20] Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med 2019;25:1706–14.
[21] Aldhaam NA, Elsayed AS, Jing Z, et al. Neoadjuvant chemotherapy is not associated with adverse perioperative outcomes after robot-assisted radical cystectomy: a case for increased use from the IRCC. J Urol 2020;203:57–61.
[22] Briganti A, Gandaglia G, Scuderi S, et al. Surgical safety of radical cystectomy and pelvic lymph node dissection following neoadjuvant pembrolizumab in patients with bladder cancer: prospective assessment of perioperative outcomes from the PURE-01 trial. Eur Urol 2020;77:576–80.
[23] Vetterlein MW, Klemm J, Gild P, et al. Improving estimates of perioperative morbidity after radical cystectomy using the European Association of Urology quality criteria for standardized reporting and introducing the comprehensive complication index. Eur Urol 2020;77:55–65.
[24] Elsayed AS, Aldhaam NA, Brownell J, et al. Perioperative and oncological outcomes of robot-assisted radical cystectomy in octogenarians. J Geriatr Oncol 2020;11:727–30.
[25] Elsayed A.S., Aldhaam N.A., Jing Z., et al. The effect of complexity of the surgical field on perioperative outcomes of robot-assisted radical cystectomy. Urology. In press. https://doi.org/10.1016/j.urology.2020.03.033.
[26] Leal Ghezzi T, Campos Corleta O. 30 years of robotic surgery. World J Surg 2016;40:2550–7.
[27] Gandaglia G, Larcher A, Gallina A, Fossati N, Briganti A, Montorsi F. Requiem for open radical cystectomy in bladder cancer patients. Eur Urol Oncol 2019;2:196–7.
[28] Bruins HM, Veskimäe E, Hernández V, et al. the importance of hospital and surgeon volume as major determinants of morbidity and mortality after radical cystectomy for bladder cancer: a systematic review and recommendations by the European Association of Urology Muscle-invasive and Metastatic Bladder Cancer Guideline Panel. Eur Urol Oncol 2020;3:131–44.
[29] Williams SB, Ray-Zack MD, Hudgins HK, et al. Impact of centralizing care for genitourinary malignancies to high-volume providers: a systematic review. Eur Urol Oncol 2019;2:265–73.
[30] Zamboni S, Soria F, Mathieu R, et al. Differences in trends in the use of robot-assisted and open radical cystectomy and changes over time in peri-operative outcomes among selected centres in North America and Europe: an international multicentre collaboration. BJU Int 2019;124:656–64.
[31] Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet 2016;388:1057–66.
[32] Peyronnet B, Seisen T, Oger E, et al. Comparison of 1800 robotic and open partial nephrectomies for renal tumors. Ann Surg Oncol 2016;23:4277–83.
[33] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[34] Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67:913–24.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion – Reply

Reply to Francesco Montorsi, Marco Bandini, Alberto Briganti, et al. Re-establishing the Role of Robot-assisted Radical Cystectomy After the 2020 EAU Muscle-invasive and Metastatic Bladder Cancer Guideline Panel Recommendations. Eur Urol 2020;78:489–91

Can Open and Robotic Radical Cystectomy be Considered Equally Effective in 2020?

J. Alfred Witjes [a,*], *Maria J. Ribal* [b], *Antoine G. van der Heijden* [a]

[a] *Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [b] *Department of Urology, Hospital Clinic, University of Barcelona, Barcelona, Spain*

We thank this large and prominent group of robotic experts for their comments [1] on the scientific summary of the updated version of the European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer [2], published in this issue of *European Urology*. First, as this document presents a summary of a very large underlying document, not all details can be addressed. Table 12 in [2] (presented as Table 1 here) clearly describes the evidence level of the currently available evidence for robot-assisted radical cystectomy (RARC), which, alongside the recommendations, is referred to by Montorsi et al [1].

We do acknowledge, however, that evidence statement 7 in Table 13 [2] ("laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open RC."), although with a level of evidence of only 3, should have been adapted since it is not aligned with Table 12 [2], so in that respect Montorsi et al are correct.

In addition, the second part of the sentence "current best practice is open radical cystectomy" (ORC) might read "current best practice is radical cystectomy", although then, rightfully, the advocates of multimodal treatment might comment on this (see Table 16 in [2]).

In conclusion, the options for treatment of nonmetastatic muscle-invasive bladder cancer include ORC and RARC, as well as multimodal treatment, and therefore we would like to rephrase the last sentence of Montorsi et al [1] as follows: "the specialist's understanding of the disease process, technical skills, and overall experience should be the main deciding factors when discussing treatment options for nonmetastatic invasive bladder cancer with patients".

This being said, we would like to make three comments about the equivalence of ORC and RARC. Addressing oncological outcomes, one would not expect significant differences in oncological outcomes between the two procedures, since the bladder and lymph nodes are taken out in both and the follow-up for RARC series is still shorter than for ORC series. One of the older studies with longer-term follow up, a large phase 3 trial comparing radiotherapy or cystectomy with and without neoadjuvant chemotherapy, showed decreasing metastasis-free survival, locoregional disease–free survival, and disease-free survival far beyond 5 yr of follow-up in all four arms [3]. In their review, Satkunasivam et al [4] based their conclusion about disease recurrence equivalence on 458 participants from only three out of the five studies included. The median follow-up in these studies was 4.9 yr in a trial not powered for this endpoint [5], 12 mo [6], and 2-yr progression-free survival [7]. Rightfully, the authors considered "the quality of evidence for this outcome to be moderate". This reminds us of the hype around "total" androgen blockade for metastatic prostate cancer in the 1980s, which in the end failed to show a survival advantage.

A second point of attention is the fact that not all countries and centres have access to a robot, and those that do have a robot will first have to pass their learning curve. In that sense RARC cannot universally be considered as the standard of care.

A third point of concern is the costs for RARC. Although these will differ by country and situation, the price of the robot is certainly not the only factor that plays a role. Unfortunately, quality studies addressing cost-effectiveness are still lacking, but a recent paper that also investigated this aspect should shed some light on this issue [8].

In conclusion, the current literature does not show significant differences in outcomes after ORC and RARC, leaving, as Montorsi et al elegantly state, informed patients with the choice of their preferred approach, as long as this

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.035.
* Corresponding author. Department of Urology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3613735; Fax: +31 24 3635114.
E-mail address: fred.witjes@radboudumc.nl (J.A. Witjes).

https://doi.org/10.1016/j.eururo.2020.07.006

Table 1 – Summary of evidence and recommendations for laparoscopic/robotic-assisted laparoscopic cystectomy.

Summary of evidence	LE
RARC has longer operative time (1–1.5 h) and major costs, but shorter length of hospital stay (1–1.5 d) and less blood loss compared to ORC.	1
Retrospective RARC series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-d complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and quality of life, are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, and not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems underutilised, and functional results of intracorporeally constructed neobladders should be studied.	4
Recommendations	**Strength rating**
Inform the patient of the advantages and disadvantages of ORC and RARC to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

LE = level of evidence; ORC = open radical cystectomy; RARC = robotic-assisted radical cystectomy.

choice is made between surgeons with similar experience in the two techniques. As a consequence, radical cystectomy, whether ORC or RARC, should be performed only in high-volume centres where, as noted, a robotic platform is commonly available and used on a daily basis.

Conflicts of interest: J. Alfred Witjes is a company consultant for Spectrum, Tocagen, BioClin, Sanofi Aventis, Biocancell, and Nucleix; has received honoraria or consultation fees from Taris Biomedical, BMS, MSD Global Medical Affairs, and Roche Nederland BV; and has participated in trials run by Taris, Cepheid, Arquer, and MEL Amsterdam. Maria J. Ribal has received company speaker honoraria from Janssen Laboratories, Olympus Iberia SAU, Astellas Pharma SA, and Ipsen Pharma; and has an interest in a patent held by Fina Biotech SLU for a method for noninvasive diagnosis of bladder cancer (European Patent Office number 13382030.8-1403). Antoine G. van der Heijden has nothing to disclose.

References

[1] Montorsi F, Bandini M, Briganti A, et al. Re-establishing the role of robot-assisted radical cystectomy after the 2020 EAU Muscle-invasive and Metastatic Bladder Cancer Guideline Panel recommendations. Eur Urol 2020;78:489–91.

[2] Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guideline. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.03.055.

[3] International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171–7.

[4] Satkunasivam R, Tallman CT, Taylor JM, Miles BJ, Klaassen Z, Wallis CJD. Robot-assisted radical cystectomy versus open radical cystectomy: a meta-analysis of oncologic, perioperative, and complication-related outcomes. Eur Urol Oncol 2019;2:443–7.

[5] Bochner BH, Dalbagni G, Marzouk KH, et al. Randomized trial comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: oncologic outcomes. Eur Urol 2018;74:465–71.

[6] Khan MS, Omar K, Ahmed K, et al. Long-term oncological outcomes from an early phase randomised controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy (CORAL). Eur Urol 2020;77:110–8.

[7] Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet 2018;391:2525–36.

[8] Wijburg CJ, Michels CTJ, Oddens JR, Grutters JPC, Witjes JA, Rovers MM. Robot assisted radical cystectomy versus open radical cystectomy in bladder cancer (RACE): study protocol of a non-randomized comparative effectiveness study. BMC Cancer 2018;18:861.

EUROPEAN UROLOGY 78 (2020) 494–497

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Prostate Cancer Risk by *BRCA2* Genomic Regions

Tommy Nyberg[a,*], *Debra Frost*[a], *Daniel Barrowdale*[a], *D. Gareth Evans*[b], *Elizabeth Bancroft*[c,d], *Julian Adlard*[e], *Munaza Ahmed*[f], *Julian Barwell*[g], *Angela F. Brady*[h], *Carole Brewer*[i], *Jackie Cook*[j], *Rosemarie Davidson*[k], *Alan Donaldson*[l], *Jacqueline Eason*[m], *Helen Gregory*[n], *Alex Henderson*[o], *Louise Izatt*[p], *M. John Kennedy*[q,r], *Claire Miller*[s], *Patrick J. Morrison*[t], *Alex Murray*[u], *Kai-Ren Ong*[v], *Mary Porteous*[w], *Caroline Pottinger*[x], *Mark T. Rogers*[y], *Lucy Side*[z], *Katie Snape*[aa], *Vishakha Tripathi*[p], *Lisa Walker*[bb], *Marc Tischkowitz*[cc], *Rosalind Eeles*[c,d], *Douglas F. Easton*[a,†], *Antonis C. Antoniou*[a,†]

[a] *Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK;* [b] *Manchester Regional Genetics Service, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK;* [c] *Oncogenetics Team, Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK;* [d] *Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, London, UK;* [e] *Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK;* [f] *North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Trust, London, UK;* [g] *Leicestershire Clinical Genetics Service, University Hospitals of Leicester NHS Trust, Leicester, UK;* [h] *North West Thames Regional Genetics Service, London North West University Healthcare NHS Trust, London, UK;* [i] *Peninsula Clinical Genetics Service, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK;* [j] *North Trent Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, Sheffield, UK;* [k] *West of Scotland Regional Genetics Service, NHS Greater Glasgow and Clyde, Glasgow, UK;* [l] *South Western Regional Genetics Service, University Hospitals Bristol NHS Foundation Trust, Bristol, UK;* [m] *Nottingham Centre for Medical Genetics, Nottingham University Hospitals NHS Trust, Nottingham, UK;* [n] *North of Scotland Regional Genetics Service, NHS Grampian, Aberdeen, UK;* [o] *Northern Genetics Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK;* [p] *South East Thames Regional Genetics Service, Guy's and St Thomas' NHS Foundation Trust, London, UK;* [q] *St James's Hospital, Dublin, Republic of Ireland;* [r] *National Centre for Medical Genetics, Dublin, Republic of Ireland;* [s] *Merseyside and Cheshire Clinical Genetics Service, Liverpool Women's NHS Foundation Trust, Liverpool, UK;* [t] *Northern Ireland Regional Genetics Service, Belfast Health and Social Care Trust, Belfast, UK;* [u] *Medical Genetics Services for Wales, Abertawe Bro Morgannwg University Health Board, Swansea, UK;* [v] *West Midlands Regional Genetics Service, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK;* [w] *South East of Scotland Regional Genetics Service, NHS Lothian, Edinburgh, UK;* [x] *Medical Genetics Services for Wales, Betsi Cadwaladr University Health Board, Bodelwyddan, UK;* [y] *All Wales Medical Genetics Service, NHS Wales, Cardiff, UK;* [z] *Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK;* [aa] *South West Thames Regional Genetics Service, St George's University Hospitals NHS Foundation Trust, London, UK;* [bb] *Oxford Regional Genetics Service, Oxford University Hospitals NHS Foundation Trust, Oxford, UK;* [cc] *Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK*

Article info

Article history:
Accepted May 5, 2020

Associate Editor:
T. Morgan

Statistical Editor:
Andrew Vickers

Abstract

A *BRCA2* prostate cancer cluster region (PCCR) was recently proposed (c.7914 to 3′) wherein pathogenic variants (PVs) are associated with higher prostate cancer (PCa) risk than PVs elsewhere in the *BRCA2* gene. Using a prospective cohort study of 447 male *BRCA2* PV carriers recruited in the UK and Ireland from 1998 to 2016, we estimated standardised incidence ratios (SIRs) compared with population incidences and assessed variation in risk by PV location. Carriers of PVs in the PCCR had a PCa SIR of 8.33 (95% confidence interval [CI] 4.46–15.6) and were at a higher risk of PCa than carriers of other *BRCA2* PVs (SIR = 3.31, 95% CI 1.97–5.57; hazard ratio = 2.34, 95% CI 1.09–5.03). PCCR PV

† These authors contributed equally.
* Corresponding author. Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, UK. Tel.: +44 (0)1223 748646; Fax: +44 (0)1223 748628.
E-mail address: ten25@medschl.cam.ac.uk (T. Nyberg).

https://doi.org/10.1016/j.eururo.2020.05.005

Keywords:
BRCA2
Genetic risk
Genomic region
Prospective cohort study
Prostate cancer

carriers had an estimated cumulative PCa risk of 44% (95% CI 23–72%) by the age of 75 yr and 78% (95% CI 54–94%) by the age of 85 yr. Our results corroborate the existence of a PCCR in *BRCA2* in a prospective cohort.

Patient summary: In this report, we investigated whether the risk of prostate cancer for men with a harmful mutation in the *BRCA2* gene differs based on where in the gene the mutation is located. We found that men with mutations in one region of *BRCA2* had a higher risk of prostate cancer than men with mutations elsewhere in the gene.

We recently reported prostate cancer (PCa) risk estimates for pathogenic variants (PVs) in *BRCA2*, based on a prospective cohort of male carriers [1]. Variability in cancer risks due to genotype-phenotype correlations may allow for more individualised counselling and screening. We noted that PVs within the so-called ovarian cancer cluster region (OCCR) in exon 11 of the gene [2–4] were associated with a lower PCa risk than other *BRCA2* PVs [1,3,4]. PVs in the OCCR have consistently been shown to be associated with an increased ovarian cancer risk but a decreased breast cancer risk [2,3,5,6], although the precise boundaries of the OCCR [3,5] and the mechanisms behind this risk variation remain uncertain. It has been proposed that the likelihood that a PV triggers nonsense-mediated mRNA decay varies by genomic region [7,8] so that OCCR PVs might produce a truncated or alternatively spliced protein the capability of which to suppress tumours varies by cancer type [2,3,5,7,8], but there is currently no experimental support for this hypothesis [7]. Shortly after the publication of our manuscript, Patel and coworkers [8] proposed the existence of a prostate cancer cluster region (PCCR) at the 3′ end of *BRCA2*, based on retrospective cohort data. This retrospective study reported that men with *BRCA2* PVs in the proposed PCCR have a higher risk of PCa (hazard ratio [HR] = 1.78, 95% confidence interval [CI] 1.25–2.52), particularly Gleason score ≥8 PCa (HR = 3.11, 95% CI 1.63–5.95), than men with PVs in the reference region c.1001 to c.7913, but did not present estimates of the absolute PCa risk for PCCR PV carriers [8]. In order to substantiate or refute this association, and to provide direct estimates of the absolute risk of PCa for carriers of *BRCA2* PCCR PVs, we have reanalysed our prospective data.

The prospective cohort comprised 447 male *BRCA2* PV carriers who were recruited to the EMBRACE study (http://ccge.medschl.cam.ac.uk/embrace/) through clinical genetics centres in the UK and Ireland between 1998 and 2016 at a median age of 51.4 yr (interquartile range 41.5–63.6 yr). The participants were counselled with regard to their PV. Detailed information on the cohort and on inclusion criteria, data collection, follow-up, and statistical analysis approach is available in our recent publication [1]. The participants' PVs (listed in Supplementary Table S1) were grouped on the basis of position within the *BRCA2* gene, based on the proposed PCCR (c.7914 to 3′ [8]; HGVS nomenclature [http://varnomen.hgvs.org/]; using cDNA reference sequence NM_000059.3 and reference genome hg18) and the wide definition of the OCCR (c.2831 to c.6401) [1–4]. We additionally considered the region bounded by c.756 and c.1000 in which Patel and coworkers [8] found evidence of an increased PCa risk, but due to a small sample size ($n = 1$) we could not estimate the PCa risk associated with this region. Here, we also present floating absolute risks (FARs) [9] to enable risk comparisons between any of the considered genomic regions.

The Anglia and Oxford Medical Research and Ethics Committee approved the study. All participants provided written informed consent.

Twenty-six participants developed PCa during a median follow-up of 5.3 yr (interquartile range 2.6–8.9 yr) [1]. Carriers of PVs in the PCCR ($n = 93$) had a PCa standardised incidence ratio (SIR) of 8.33 (95% CI 4.46–15.6), whereas carriers of PVs elsewhere in *BRCA2* ($n = 354$) had an SIR of 3.31 (95% CI 1.97–5.57) compared with population incidences. This corresponds to a significantly higher PCa risk associated with PVs in the PCCR than PVs not in the PCCR (HR = 2.34, 95% CI 1.09–5.03; Table 1). Compared with PVs in the region c.1001 to c.7913 [8], PCCR PVs were associated with an HR of 2.09 (95% CI 0.98–4.45). As previously reported, the SIR for carriers of PVs in the wide definition of the OCCR ($n = 178$) was 2.46 (95% CI 1.07–5.64) [1], and the risk for carriers of PCCR PVs was also significantly higher than that for OCCR PV carriers (HR = 3.41, 95% CI 1.27–9.16). The SIR for PVs located in the region bounded by the OCCR and the PCCR (c.6402 to c.7913; $n = 66$) was estimated to be 6.14 (95% CI 2.18–17.3), and the SIR for *BRCA2* PVs upstream of the OCCR (5′ to c.2830; $n = 108$) was 3.50 (95% CI 1.48–8.26). The FARs for the comparison of risks across the four regions suggested that the observed increased risk associated with PVs in the PCCR may partly be driven by the lower risk associated with PVs in the OCCR (Table 1). The proportional hazard assumption was violated for the model with all genomic regions fitted (Schoenfeld residual test, $p = 0.003$); in line with this the corresponding Kaplan-Meier plot indicated that the risks might be similar between OCCR and PCCR PV carriers at younger ages but deviate at older ages. PCCR PV carriers had an estimated cumulative PCa risk of 44% (95% CI 23–72%) by the age of 75 yr and 78% (95% CI 54–94%) by 85 yr. After omitting the first 6 mo of follow-up to assess the possible effect of screening-associated diagnoses of indolent PCa, the corresponding estimates were 41% (95% CI 20–73%) and 69% (95% CI 42–91%), respectively (Fig. 1).

The difference in PCa risk for PVs in the PCCR versus that in the OCCR remained statistically significant after adjusting

Table 1 – Prostate cancer risk by location of *BRCA2* pathogenic variant.

PV location	*N*	Person years	Observed events	Incidence rate per 1000 person years (95% CI)	Expected events	SIR (95% CI)	HR (95% CI)	FAR (95% CI)
Compared with non-PCCR PVs								
Non-PCCR (5′ to c.7913)	354	2029.8	15	7.39 (4.45–12.3)	4.53	3.31 (1.97–5.57)	Reference	
PCCR (c.7914 to 3′)	93	524.6	11	21.0 (11.4–38.7)	1.32	8.33 (4.46–15.6)	2.34 (1.09–5.03)	
Compared with OCCR PVs								
5′ to c.2830	108	625.8	5	7.99 (3.37–19.0)	1.43	3.50 (1.48–8.26)	1.72 (0.50–5.94)	1.72 (0.70–4.24)
OCCR (c.2831 to c.6401) [a]	178	1054.4	6	5.69 (2.54–12.8)	2.44	2.46 (1.07–5.64)	Reference	1.00 (0.43–2.33)
c.6402 to c.7913	66	338.8	4	11.8 (4.29–32.5)	0.65	6.14 (2.18–17.3)	3.23 (0.79–13.2)	3.23 (1.15–9.11)
PCCR (c.7914 to 3′)	93	524.6	11	21.0 (11.4–38.7)	1.32	8.33 (4.46–15.6)	3.41 (1.27–9.16)	3.41 (1.96–5.95)
Indeterminable	2							

CI = confidence interval; FAR = floating absolute risk; HR = hazard ratio; OCCR = ovarian cancer cluster region; PCCR = prostate cancer cluster region; PV = pathogenic variant; SIR = standardised incidence ratio.
[a] Detailed results for carriers of PVs in the OCCR are available in a previous publication [1].

for family history of PCa (number of first- and second-degree relatives diagnosed with PCa; adjusted HR = 3.00, 95% CI 1.06–8.54) or geographical location (adjusted HR = 3.79, 95% CI 1.41–10.2). This difference remained similar after omitting the first 6 mo of follow-up (HR = 3.96, 95% CI 1.18–13.3), related individuals (HR = 4.29, 95% CI 1.30–14.2), and carriers of PVs in the region c.756 to c.1000 (HR = 3.42, 95% CI 1.27–9.18) or missense variants (HR = 3.76, 95% CI 1.36–10.4). When carriers of the Ashkenazi founder PV c.5946delT (n = 42), which is located in the OCCR, was omitted, the difference in PCa risk between PCCR and OCCR PV carriers was not statistically significant, but the HR estimate was of similar magnitude (HR = 2.89, 95% CI 0.98–8.53; Supplementary Table S2).

We did not observe a higher risk of Gleason score ≥8 PCa for PVs in the PCCR than for PVs not in the PCCR (HR = 0.87, 95% CI 0.12–6.34) or in the region c.1001 to c.7913 (HR = 0.79, 95% CI 0.11–5.69). However, the HRs did not differ significantly from those for Gleason score ≤7 PCa (PCCR vs non-PCCR: HR = 3.32, 95% CI 1.25–8.84; test for heterogeneity, p = 0.052; PCCR vs c.1001 to c.7913: HR = 2.94, 95% CI 1.11–7.80; test for heterogeneity, p = 0.088).

Our results corroborate the observation that carriers of PVs in the PCCR of the *BRCA2* gene [8] are at a higher risk of PCa than other *BRCA2* PV carriers. Patel and coworkers [8] reported an HR of 1.78 (95% CI 1.25–2.52) compared with PVs in the region c.1001 to c.7913, consistent with our HR estimate of 2.09 (95% CI 0.98–4.45). Our findings do not support a stronger association with a more aggressive phenotype, but these estimates were based on a small number of cases and the associated CIs are wide. PV carriers may receive enhanced screening, which may lead to biases in comparisons against the population incidence [1]. However, current screening practices do not differ by *BRCA2* PV

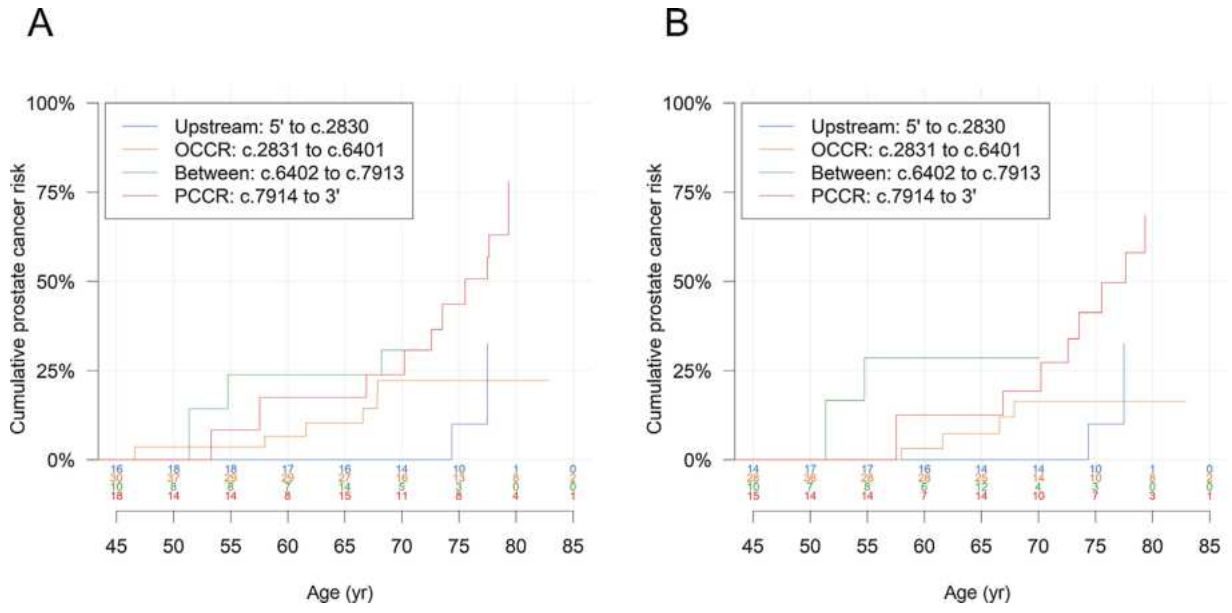


Fig. 1 – Absolute prostate cancer risk (A) by location of *BRCA2* pathogenic variant and (B) by location of *BRCA2* pathogenic variant and with follow-up initiated 6 mo after study entry. The number at risk at each age is shown above the *x*-axis. The curves are truncated at ages when fewer than five participants are at risk. OCCR = ovarian cancer cluster region; PCCR = prostate cancer cluster region.

location, and so this is unlikely to have confounded the comparisons between the *BRCA2* genomic regions. A much larger cohort of unaffected carriers with longer follow-up is required to provide more precise PV-specific risk estimates and to further clarify whether the observed variation in risk reflects lower risks associated with PVs outside the OCCR and PCCR than the risk associated with PCCR PVs, or solely a lower risk associated with PVs in the OCCR.

***Author contributions*:** Tommy Nyberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Antoniou, Nyberg, Easton.
Acquisition of data: Frost, Barrowdale, Bancroft, Easton, Eeles, Evans, Tischkowitz, Adlard, Ahmed, Barwell, Brady, Brewer, Cook, Davidson, Donaldson, Eason, Gregory, Henderson, Izatt, Kennedy, Miller, Morrison, Murray, Ong, Porteous, Pottinger, Rogers, Side, Snape, Tripathi, Walker.
Analysis and interpretation of data: Nyberg, Antoniou, Easton.
Drafting of the manuscript: Nyberg, Antoniou, Easton.
Critical revision of the manuscript for important intellectual content: Evans, Frost, Barrowdale, Bancroft, Eeles, Tischkowitz, Adlard, Ahmed, Barwell, Brady, Brewer, Cook, Davidson, Donaldson, Eason, Gregory, Henderson, Izatt, Kennedy, Miller, Morrison, Murray, Ong, Porteous, Pottinger, Rogers, Side, Snape, Tripathi, Walker.
Statistical analysis: Nyberg, Antoniou, Easton.
Obtaining funding: Easton, Antoniou, Eeles, Evans.
Administrative, technical, or material support: Frost, Barrowdale, Bancroft.
Supervision: Antoniou, Tischkowitz.
Other: None.

Financial disclosures: Tommy Nyberg certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This work was supported by Cancer Research UK grants C12292/A20861 and C12292/A22820. EMBRACE was supported by Cancer Research UK grants C1287/A23382 and C1287/A26886. D. Gareth Evans is supported by a National Institute for Health Research grant to the Biomedical Research Centre, Manchester (IS-BRC-1215-20007). Rosalind Eeles is supported by Cancer Research UK grant C5047/A8385, and by National Institute for Health Research support to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust.

***Acknowledgements*:** We thank all the participants in the EMBRACE study. The data used in the analysis are available to other researchers upon request to the EMBRACE study coordinators (https://ccge.medschl.cam.ac.uk/embrace/).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.05.005.

References

[1] Nyberg T, Frost D, Barrowdale D, et al. Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Eur Urol 2020;77:24–35.
[2] Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the *BRCA2* gene. Nat Genet 1997;15:103–5.
[3] Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001;68:410–9.
[4] van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711–9.
[5] Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA 2015;313:1347–61.
[6] Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–16.
[7] Ware MD, DeSilva D, Sinilnikova OM, Stoppa-Lyonnet D, Tavtigian SV, Mazoyer S. Does nonsense-mediated mRNA decay explain the ovarian cancer cluster region of the BRCA2 gene? Oncogene 2006;25:323–8.
[8] Patel VL, Busch EL, Friebel TM, et al. Association of genomic domains in BRCA1 and BRCA2 with prostate cancer risk and aggressiveness. Cancer Res 2020;80:624–38.
[9] Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med 1991;10:1025–35.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence – Editor's Choice

Stool Microbiome Profiling of Patients with Metastatic Renal Cell Carcinoma Receiving Anti–PD-1 Immune Checkpoint Inhibitors

Nicholas J. Salgia [a,†], *Paulo G. Bergerot* [a,†], *Manuel Caitano Maia* [b,†], *Nazli Dizman* [a], *JoAnn Hsu* [a], *John D. Gillece* [c], *Megan Folkerts* [c], *Lauren Reining* [c], *Jeffrey Trent* [d], *Sarah K. Highlander* [c,*], *Sumanta K. Pal* [a,*]

[a] *Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA;* [b] *Centro de Oncologia do Paraná, Curitiba, Brazil;* [c] *Pathogen and Microbiome Division, Translational Genomics Research Institute North, Flagstaff, AZ, USA;* [d] *Translational Genomics Research Institute, Phoenix, AZ, USA*

Article info

Article history:
Accepted July 11, 2020

Associate Editor:
T. Morgan

Keywords:
Bacteriomic profiling
Checkpoint inhibitor
Microbiome
Nivolumab
Renal cell carcinoma

Abstract

Preclinical models and early clinical data suggest an interplay between the gut microbiome and response to immunotherapy in solid tumors including metastatic renal cell carcinoma (mRCC). We sought to characterize the stool microbiome of mRCC patients receiving a checkpoint inhibitor (CPI) and to assess treatment-related changes in microbiome composition over the course of CPI therapy. Stool was collected from 31 patients before initiation of nivolumab (77%) or nivolumab plus ipilimumab (23%) therapy, of whom 58% experienced clinical benefit. Greater microbial diversity was associated with clinical benefit from CPI therapy ($p = 0.001$), and multiple species were associated with clinical benefit or lack thereof. Temporal profiling of the microbiome indicated that the relative abundance of *Akkermansia muciniphila* increased in patients deriving clinical benefit from CPIs. This study substantiates results from previous CPI-related microbiome profiling studies in mRCC. Temporal changes in microbiome composition suggest potential utility in modulating the microbiome for more successful CPI outcomes.

Patient summary: We compared the composition and diversity of the gut microbiome in patients receiving immunotherapy for renal cell carcinoma. We found that higher microbial diversity is associated with better treatment outcomes. Treatment response is characterized by changes in microbial species over the course of treatment.

† These authors contributed equally to this work.
* Corresponding authors. City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, USA. Tel.: +1 626 2562673; Fax: +1 626 3018233. Translational Genomics Research Institute North, 3051 West Shamrell Boulevard, Flagstaff, AZ 86005, USA. Tel.: +1 928 2136996; Fax: +1 928 2136996.
E-mail addresses: shighlander@tgen.org (S.K. Highlander), spal@coh.org (S.K. Pal).

For patients with metastatic renal cell carcinoma (mRCC) it remains unclear who will experience clinical benefit with checkpoint inhibitors (CPIs) and why, so there is a need for clinically validated biomarkers. Studies using somatic genomic sequencing have revealed alterations in individual genes (eg, *PBRM1*) and genomic signatures (eg, myeloid inflammatory gene expression) as predictive of response to CPIs in mRCC [1]. Recent data further indicate that the gut

https://doi.org/10.1016/j.eururo.2020.07.011
0302-2838/

microbiome plays a role in dictating immunotherapy response. Vetizou et al [2] reported that anti–CTLA-4 activity in melanoma murine models depends on the presence of *Bacteroides* spp., while Sivan and colleagues [3] showed that the activity of anti–PD-L1 agents is correlated with *Bifidobacterium* spp. Clinical work in melanoma implicates Ruminococcaceae, *Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium*, and *Faecalibacterium* spp. in therapeutic response to CPIs [4–6]. In the context of RCC and non–small-cell lung cancer, Routy et al [7] demonstrated that resistance to CPIs can be modulated by an abnormal gut microbiome composition; the abundance of *Akkermansia* spp. in patients' stool at the time of diagnosis is associated with clinical response to CPIs.

We conducted a prospective observational study to determine the association between baseline gut microbial diversity and clinical benefit in patients with mRCC receiving CPIs (nivolumab monotherapy or nivolumab with ipilimumab). Patients with pathologically confirmed mRCC according to standard criteria (American Joint Committee on Cancer CC 7th edition) set to receive a standard-of-care nivolumab-based regimen were eligible for this study. Key exclusion criteria included gastrointestinal comorbidities such as irritable bowel syndrome or the use of antibiotics within 14 d of enrollment. The protocol and informed consent form were approved by an institutional review board.

Patients were followed for the first 3 mo of CPI therapy for specimen and data collection. Patients were asked to provide three stool collections (baseline, 1 mo, and 3 mo) and three blood samples (to be assessed in future studies). All patients agreed to refrain from intake of yogurt or other bacteria-fortified foods (including supplemental probiotics) for 3 mo after enrollment. Response to CPIs was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST v1.1 criteria. On the basis of radiographic response, patients were classified as experiencing clinical benefit (CR, PR, or SD > 4 mo) or no clinical benefit (PD). Gut microbiota composition was assessed using whole-genome shotgun metagenomic sequencing [8]. An overview of the laboratory and computational methods is provided in the Supplementary material.

Between February 2017 and May 2019, 31 patients were enrolled; Supplementary Table 1 lists the patient characteristics. Within the cohort, 11 patients (35%) achieved CR or PR and seven patients (23%) achieved SD of at least 4 mo. All 31 patients provided a baseline stool sample within the 7 d before CPI initiation, for which whole-metagenome sequencing was performed. A total of 26 patients (84%) submitted at least one follow-up stool sample at a median of 28 d following CPI initiation (interquartile range 25–37 d). Twelve patients (39%) also provided a third stool sample a median of 79 d into therapy (interquartile range 57–84 d). Bray-Curtis hierarchical cluster analysis revealed differences in microbiome profile between the clinical benefit and no clinical benefit groups (Supplementary Fig. 1). LEfSe identified 13 bacterial species with a linear discriminant analysis (LDA) score of ≥3 that distinguished between patients who experienced clinical benefit and those who did not (Fig. 1) using stool collected across all time points. Species with the greatest significance among patients with clinical benefit were *Bifidobacterium adolescentis* ($p = 0.002$), *Barnesiella intestinihominis* ($p = 0.002$), *Odoribacter splanchnicus* ($p = 0.006$), and *Bacteroides eggerthii* ($p = 0.009$). Patients experiencing clinical benefit had greater alpha diversity according to the Shannon index ($p = 0.001$) using stool collected across all time points (Fig. 2A,B).

Phylogenetic diversity was quantified for each patient across collection time points. Taxa bar plots in Fig. 2C depict patient-specific changes in microbiome composition between time points on CPI regimens. Among patients experiencing clinical benefit, the relative abundance of *Akkermansia* spp. generally increased across the CPI therapy timeline. Patients 4, 16, 30, 31, and 39 are among those representative of this phenomenon. In addition, patients 20,

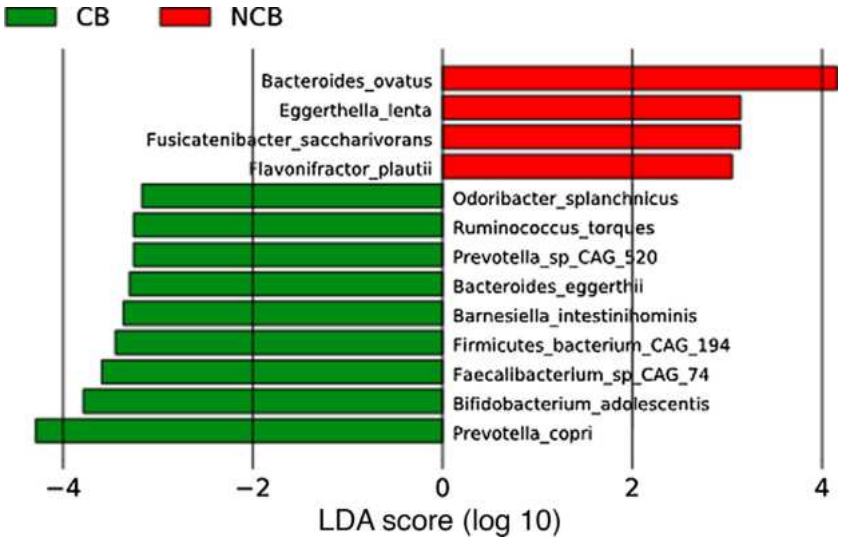


Fig. 1 – Top organisms of significance by response with a linear discriminant analysis (LDA) score of >3 as determined using LEfSe. CB = clinical benefit; NCB = no clinical benefit.

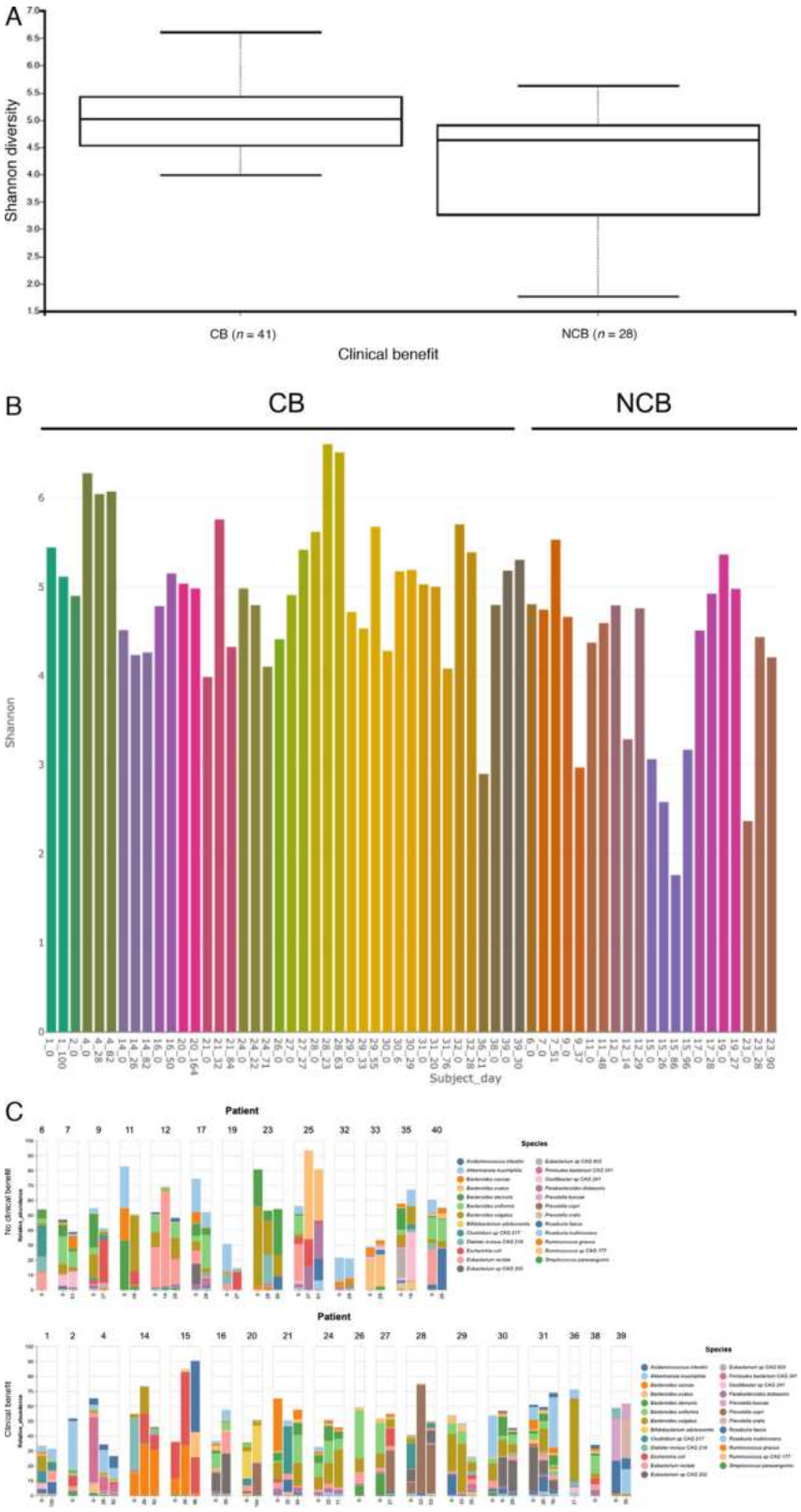


Fig. 2 – (A) Boxplot of alpha diversity (Shannon diversity index) for patients with clinical benefit (CB) or no clinical benefit (NCB); $p = 0.001$, Kruskal-Wallis test. (B) Shannon diversity index for all patient samples across all time points. (C) Bar plots of top taxa depicting temporal differences in bacteriomic profiles among patients with CB or NCB with checkpoint inhibitor use.

27, and 28 (who all derived clinical benefit) demonstrated increases in the abundance of *Prevotella copri* while on CPI therapy.

Our results represent the first US-based study seeking an association between microbiome composition and immunotherapy response in mRCC patients. The novelty of the study design lies in sequential profiling of the microbiome. These results suggest that certain species (eg, *P. copri*) appear to expand in relative abundance in patients deriving clinical benefit. Interestingly, *Akkermansia muciniphila* increased in relative abundance in many patients deriving clinical benefit, but decreased in relative abundance in many patients not deriving clinical benefit. Although we did not find an association between baseline *A. muciniphila* and clinical benefit, this has been implicated in a previous study [7].

Limitations of the study include the method of stool collection. Stool was collected in a small, non–vacuum-sealed container, so propagation of aerobic bacteria was possible. Collection of stool specimens at distal time points was also challenging. At 4 wk, for instance, only 19 patients (63%) submitted stool specimens as mandated by the study protocol. This could reflect a subset of patients who progressed, but most patients were simply noncompliant with the submission schedule. Our study also encompassed a broad line-of-therapy range. The approval of nivolumab with ipilimumab in April 2018 shifted accrual towards a more substantial proportion of patients receiving this combination in the frontline setting. It is important to note that only 50% of patients on nivolumab monotherapy experienced clinical benefit, whereas 86% of those receiving combination therapy achieved a benefit. Another limitation to consider is our approach of combining specimens across time points. We feel that this approach is justified as the intrapatient heterogeneity within our cohort (as demonstrated in Fig. 2A–C) was limited as compared to the interpatient heterogeneity.

These limitations notwithstanding, our results have led to the development of a phase 1 randomized clinical trial at our institution investigating the role of gut microbial modulation in CPI response. In this study, we are using the standard first-line regimen of nivolumab with ipilimumab, with or without CBM-588 (NCT03829111). CMB-588 is a strain of *Clostridium butyricum* with immunomodulatory and anti-inflammatory effects in the intestinal epithelium; the agent may foster the development of a more favorable microbiome, including species cited herein that are associated with CPI response [9,10].

Author contributions: Sumanta K. Pal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pal, Caitano Maia, Hsu, Highlander.
Acquisition of data: Bergerot, Dizman, Hsu, Salgia, Gillece, Folkerts, Reining, Pal, Highlander.
Analysis and interpretation of data: Bergerot, Dizman, Hsu, Salgia, Gillece, Folkerts, Reining, Pal, Highlander.
Drafting of the manuscript: Salgia, Pal.
Critical revision of the manuscript for important intellectual content: Salgia, Pal, Bergerot, Highlander, Dizman.
Statistical analysis: Dizman, Gillece, Folkerts, Reining, Highlander.
Obtaining funding: Pal, Hsu, Trent, Highlander.
Administrative, technical, or material support: Hsu, Pal, Trent, Highlander.
Supervision: Pal, Highlander, Trent.
Other: None.

Financial disclosures: Sumanta K. Pal certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: John D. Gillece, Megan Folkerts, Lauren Reining, Jeffrey Trent, and Sarah K. Highlander are employed by the Translational Genomics Research Institute. Manuel Caitano Maia has received honoraria form Astellas, Bristol-Myers Squibb, MSD, and Pfizer; consulting fees from MSD; and event sponsorship from Roche, Astellas, Pfizer, Janssen, Bristol-Myers Squibb, MSD, Bayer, and Ipsen. Sumanta K. Pal has received honoraria from Novartis, Medivation, and Astellas Pharma; has acted in a consulting or advisory role for Pfizer, Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Exelixis, Bristol-Myers Squibb, and Astellas Pharma; and has received research funding from Medivation. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: This study was supported in part by a grant from Bristol-Myers Squibb. The sponsor played a role in the design and conduct of the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.07.011.

References

[1] Kotecha RR, Motzer RJ, Voss MH. Towards individualized therapy for metastatic renal cell carcinoma. Nat Rev Clin Oncol 2019;16:621–33.
[2] Vetizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015;350:1079–84.
[3] Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084–9.
[4] Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103.
[5] Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. Science 2018;359:104–8.
[6] Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 2017;28:1368–79.
[7] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science 2018;359:91–7.

[8] Zhu Q, Dupont CL, Jones MB, et al. Visualization-assisted binning of metagenome assemblies reveals potential new pathogenic profiles in idiopathic travelers' diarrhea. Microbiome 2018;6:201.
[9] Hagihara M, Yamashita R, Matsumoto A, et al. The impact of Clostridium butyricum MIYAIRI 588 on the murine gut microbiome and colonic tissue. Anaerobe 2018;54:8–18.
[10] Hagihara M, Yamashita R, Matsumoto A, et al. The impact of probiotic Clostridium butyricum MIYAIRI 588 on murine gut metabolic alterations. J Infect Chemother 2019;25:571–7.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Maarten de Rooij, Bas Israël, Joyce G.R. Bomers, Ivo G. Schoots and Jelle O. Barentsz on pp. 512–514 of this issue

Additional Value of Dynamic Contrast-enhanced Sequences in Multiparametric Prostate Magnetic Resonance Imaging: Data from the PROMIS Study

Ahmed El-Shater Bosaily [a,b,], Elena Frangou [c], Hashim U. Ahmed [a,d,e], Mark Emberton [a,f], Shonit Punwani [a,f], Richard Kaplan [c], Louise C. Brown [c], Alex Freeman [f], Charles Jameson [f], Richard Hindley [g], Delia Peppercorn [g], Andrew Thrower [g], Mathias Winkler [e], Tara Barwick [h], Victoria Stewart [h], Nick Burns-Cox [i], Paul Burn [i], Maneesh Ghei [j], Jeevan Kumaradevan [j], Raj Prasad [k], Janice Ash-Miles [k], Iqbal Shergill [l], Sanjay Agarwal [l], Derek Rosario [m], Ferekh Salim [m], Simon Bott [n], Hywel Evans [n], Alastair Henderson [o], Sukanya Ghosh [o], Tim Dudderidge [p], J. Smart [p], Ken Tung [p], Alexander Kirkham [f], on behalf of the PROMIS Group*

[a] *Division of Surgery and Interventional Sciences, University College London, London, UK;* [b] *Department of Radiology, Royal Free NHS foundation Trust, London, UK;* [c] *The Medical Research Council, London, UK;* [d] *Imperial Prostate, Division of Surgery, Department of Surgery and Cancer, Imperial College London, London, UK;* [e] *Imperial Urology, Imperial College London Healthcare NHS Trust, London, UK;* [f] *University College Hospital NHS Foundation Trust, London, UK;* [g] *Hampshire Hospitals NHS Foundation Trust, Hampshire, UK;* [h] *Department of Radiology, Imperial College London Healthcare NHS Trust, London, UK;* [i] *Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust, Taunton, UK;* [j] *Whittington Health NHS Trust, London, UK;* [k] *North Bristol NHS Trust, Bristol, UK;* [l] *Wrexham Maelor Hospital, Wrexham, UK;* [m] *Royal Hallamshire Hospital, Sheffield, UK;* [n] *Frimley Health NHS Foundation Trust, Camberley, UK;* [o] *Maidstone and Tunbridge Wells NHS Trust, Tunbridge Wells, UK;* [p] *University Hospital Southampton NHS Foundation Trust, Southampton, UK*

Article info

Article history:
Accepted March 2, 2020

Associate Editor:
Giacomo Novara

Statistical Editor:
Melissa Assel

Keywords:
Multiparametric magnetic resonance imaging
Biparametric magnetic resonance imaging
Prostate cancer
Prostate magnetic resonance imaging

Abstract

Background: Multiparametric magnetic resonance imaging (MP-MRI) is established in the diagnosis of prostate cancer, but the need for enhanced sequences has recently been questioned.
Objective: To assess whether dynamic contrast-enhanced imaging (DCE) improves accuracy over T2 and diffusion sequences.
Design, setting, and participants: PROMIS was a multicentre, multireader trial, with, in this part, 497 biopsy-naïve men undergoing standardised 1.5T MP-MRI using T2, diffusion, and DCE, followed by a detailed transperineal prostate mapping (TPM) biopsy at 5 mm intervals. Likert scores of 1–5 for the presence of a significant tumour were assigned in strict sequence, for (1) T2 + diffusion and then (2) T2 + diffusion + dynamic contrast-enhanced images.
Outcome measurements and statistical analysis: For the primary analysis, the primary PROMIS outcome measure (Gleason score $\geq$4 + 3 or $\geq$6 mm maximum cancer length) on TPM was used, and an MRI score of $\geq$3 was considered positive.
Results and limitations: ensitivity without and with DCE was 94% and 95%, specificity 37% and 38%, positive predictive value 51% and 51%, and negative predictive value 90% and 91%, respectively ($p >$ 0.05 in each case). The number of patients avoiding biopsy (scoring 1–2) was similar (123/497 vs 121/497, $p =$ 0.8). The number of equivocal scores (3/5) was slightly higher without DCE (32% vs 28% $p =$ 0.031). The proportion of MRI equivocal (3/5) and positive (4–5) cases showing significant tumours were similar (23% and 71% vs 20% and 69%). No cases of dominant Gleason 4 or higher were missed with DCE, compared with a single case with T2 + diffusion-weighted imaging. No attempt was made to correlate lesion location on MRI and

* Corresponding author. Division of Surgery and Interventional Science, University College London, Gower Street, London WC1E6BT, UK. Tel.: +4407411938521.
E-mail address: ashater@nhs.net (A.-S. Bosaily).

https://doi.org/10.1016/j.eururo.2020.03.002

EU ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to answer questions on-line. The EU-ACME credits will then be attributed automatically.

histology, which may be considered a limitation. Radiologists were aware of the patient's prostate-specific antigen.
Conclusions: Contrast adds little when MP-MRI is used to exclude significant prostate cancer.
Patient summary: An intravenous injection of contrast may not be necessary when magnetic resonance imaging is used as a test to rule out significant tumours in the prostate.

1. Introduction

Multiparametric magnetic resonance imaging (MP-MRI) is now a well-established tool in the diagnostic pathway of suspected prostate cancer before biopsy [1]. Standards for the conduct of the study have been part of both versions of the Prostate Imaging Reporting and Data System (PIRADS) scoring systems [2,3], and in each case, have included dynamic contrast-enhanced imaging (DCE) sequences as standard in addition to T2 and diffusion-weighted imaging (DWI).

Version 2.1 of PIRADS acknowledges recent data, suggesting that the additional utility of DCE for the detection of tumour may be limited and provides a structure for reporting "biparametric" (T2 and diffusion) studies, although it does not go as far as recommending the routine exclusion of DCE [4]. One of the main reasons for retaining DCE sequences was the lack of robust data on its diagnostic accuracy from multi-institutional trials with multiple readers [4].

The PROMIS study was a large, multicentre, prospective study with the primary aim of assessing the diagnostic accuracy of prebiopsy MP-MRI using standard 1.5 T machines without an endorectal coil [5]. We report on an embedded prospective assessment of the additional value of DCE over a set of T2 and diffusion-weighted images.

2. Patients and methods

The PROMIS trial was a prospective, multicentre, paired validating cohort study reported to the Standards for Reporting Diagnostic Accuracy (STARD) [5–7]. A total of 576 biopsy-naïve men with a clinical suspicion of prostate cancer and prostate-specific antigen (PSA) <15 ng/ml underwent 1.5 T MP-MRI followed by a detailed combined biopsy, with transperineal mapping of the whole prostate at 5 mm intervals as well as the standard 12-core transrectal ultrasound (TRUS) biopsy. The methods and results are described in detail in a number of papers [5,7,8] but are summarised here.

2.1. MRI conduct and reporting

All patients received MP-MRI compliant with European Society of Uro-Radiology guidelines [2], with 1.5 T magnetic field strength and a pelvic phased-array coil. This included T2-weighted, diffusion-weighted (including a dedicated b = 1400s/mm2 sequence), and dynamic gadolinium contrast-enhanced (with an approximately 15 s time resolution) sequences (Table 1).

The radiologists from the 11 UK centres in the trial (1) had experience of reporting MP-MRI (although there was no minimum criterion for the length of experience) and (2) attended a single day-long training session. Reporting was on a standardised MRI report format (Fig. 1), with the prostate divided into 12 distinct regions of interest. In one sitting, the radiologist assigned a Likert score of 1–5 [9] for each grid point, firstly viewing the T2 images alone, then T2 + diffusion-weighted images, and finally T2+ diffusion-weighted + dynamic contrast-enhanced images, in strict sequence and with no retrospective revisions allowed. The overall score of the likelihood of tumour in each patient was defined as the maximum score within the 12 boxes of the grid for each of T2, T2 + DWI, and T2 + DWI + DCE sequences. Reporters were blind to any histological data but were aware of the patient's PSA.

2.2. Standard of reference: biopsy

The protocol allowed men with T4 disease on imaging or prostate size >100 cc to exit the trial without biopsy; otherwise, the series is consecutive. The MP-MRI report remained blinded to all other physicians and trial staff, and the combined prostate biopsy procedure was performed with no knowledge of the MP-MRI. The transperineal prostate mapping (TPM) biopsy results were used as the reference standard in the main study findings and also in this paper. Biopsy reporting was completed by one of two expert uropathologists blinded to all MR images and TRUS-biopsy findings. As in the main study, two definitions of clinically significant cancer were used (based on previous work using biopsy simulations [10]): definition 1 (primary outcome) was Gleason score ≥4 + 3 or cancer core length ≥6 mm of any grade, and definition 2 was Gleason score ≥3 + 4 or cancer core length ≥4 mm of any grade.

Table 1 – MRI parameters.

	TR	TE	Flip angle (degree)	Plane	Slice thickness, mm (gap)	Matrix size	Field of view (mm)	Time from scan
T2 TSE	5170	92	180	Axial, coronal, sagittal	3 (10% gap)	256 × 256	180 × 180	3 min 54 s (axial)
VIBE fat sat	5.61	2.52	15	Axial	3	192 × 192	260 × 260	Continue for at least 5 min 30 s after contrast
Diffusion (b values: 0, 150, 500, 1000)	2200	Min (<98)		Axial	5	172 × 172	260 × 260	5 min 44 s (16 average)
Diffusion (b = 1400)	2200	Min (<98)		Axial	5	172 × 172	320 × 320	3 min 39 s (32 average)

MRI = magnetic resonance imaging; TE = echo time; TR = repetition time.

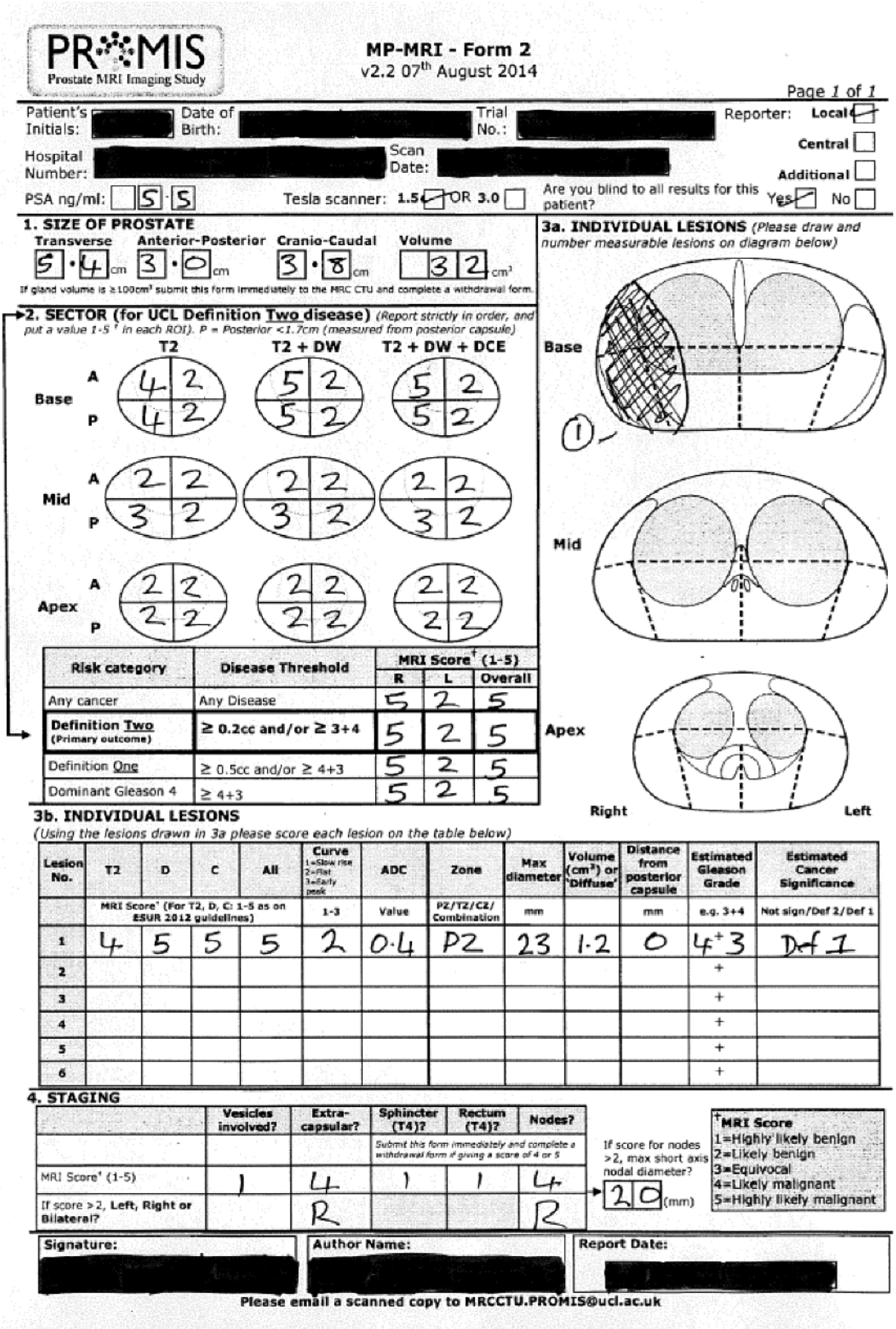


Fig. 1 – A sample PROMIS study MRI reporting form. DCE = dynamic contrast-enhanced imaging; DW = diffusion weighted; MP-MRI = multiparametric MRI; MRI = magnetic resonance imaging; UCL = University College London.

2.3. Changes from the pilot phase

For the purpose of this analysis, we included patients from the main phase of the PROMIS trial only ($n = 497$). Seventy-nine patients in the pilot phase were excluded because the sequenced reporting was for a threshold of "any tumour". This was amended so that radiologists were asked to determine whether they suspected the presence of "clinically significant cancer" (≥0.2 cc and/or Gleason score ≥3 + 4) in the main phase of the trial (see Fig. 1 for the report form).

2.4. Statistical analysis

The diagnostic accuracy of each of the three sequence combinations was assessed against multiple histological thresholds of significant disease using contingency tables. For the primary analysis, a score of ≥3 on MRI was compared with histological definition 1 of a significant tumour, which was used in the previously published primary outcome paper for PROMIS [5]. PROMIS was not powered to detect differences between sequences, and our analysis must therefore be viewed as exploratory.

Given the paired nature of the data, we used McNemar's test to analyse the differences between T2 + DWI and T2 + DWI + DCE. As it was not the main aim of the paper, and to limit the number of statistical comparisons, we did not compare the results of reporting with T2 sequences alone. To compare the positive predictive value (PPV) and negative predictive value (NPV) for the different MRI sequences against TPM biopsy, we used a general estimating equation logistic regression model [11,12], as these are dependent on the prevalence of disease. The TPM results serve as the outcome variable, while the explanatory variable is the MRI result for each individual and each sequence. For NPV, the coding logic was reversed (ie, a negative biopsy was coded as 1 and a positive biopsy was coded as 0) as the test result of interest is correct detection of the absence of clinically significant cancer on the TPM biopsy.

All analyses were done using Stata version 15.1 software (Stata Corporation, College Station, TX, USA).

3. Results

In the 497 men assessed, cancer was detected in 71% (354/497) of patients who had undergone TPM biopsies. Of all the men, 59% (293/497) had definition 2 (Gleason score ≥3 + 4 or cancer core length ≥4 mm) and 41% (203/497) had definition 1 (Gleason score ≥4 + 3 or cancer core length ≥6 mm) disease (Table 2).

Using definition 1 (Table 3), the addition of DCE to T2 + DWI did not result in statistically significant differences in sensitivity (95% with DCE vs 94% without, $p = 0.7$), specificity (38% vs 37%, $p = 0.7$), PPV (51% vs 51%, $p = 0.6$) and NPV (91% vs 90%, $p = 0.6$).

Table 2 – – Participant characteristics.

Variable	Median (interquartile range)
Age	64 (58–69)
PSA (ng/ml)	6.5 (5.0–8.8)
Cancer prevalence on biopsy	
Any cancer	71% (354/497)
Definition 1 *	41% (203/497)
Definition 2 *	59% (293/497)
Dominant Gleason pattern 4 or higher grade	11% (53/497)
Any Gleason pattern 4 disease	56% (276/497)

PSA = prostate-specific antigen.

Table 3 – Diagnostic accuracy of T2 + DWI and T2 + DWI + DCE in the detection of definition 1 clinically significant prostate cancer (≥4 + 3 or core length ≥6 mm).

MRI sequences	Diagnostic accuracy, MRI score ≥3 considered positive (with 95% confidence intervals)				Patients scoring 1 or 2 (potentially avoiding biopsy)	Proportion scoring 3/5	Proportions with MRI score 3 that were positive on biopsy	Proportions with MRI score 4–5 that were positive on biopsy
	Sens	Spec	PPV	NPV				
T2	96% (92–98)	30% (24–35)	49% (44–54)	92% (84–96)	95/497 (19%)	242/497 (49%)	77/242 (32%)	118/160 (74%)
T2 + DWI	94% (90–97)	37% (32–43)	51% (46–56)	90% (83–95)	121/497 (24%)	158/497 (32%)	37/158 (23%)	154/218 (71%)
T2 + DWI + DCE	95% (91–97)	38% (33–44)	51% (46–57)	91% (85–95)	123/497 (25%)	136/497 (28%)	27/136 (20%)	165/238 (69%)
Additional benefit of adding DCE sequence (with 95% confidence intervals)	1% (−1.8 to 3.8)	1% (−5 to 7)	0% (−6.2 to 6.2)	1% (−2.6 to 4.6)				

DCE = dynamic contrast-enhanced imaging; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

Table 4 – Diagnostic accuracy of T2, T2 + DWI, and T2 + DWI + DCE in the detection of alternate definitions of clinically significant prostate cancer.

MRI Sequence	Diagnostic accuracy			
	Sensitivity	Specificity	PPV	NPV
Definition 2: Gleason score ≥3 + 4 or cancer core length ≥4 mm				
T2	91% (88–94)	34% (28–41)	67% (62–71)	74% (64–82)
T2 + DWI	89% (85–92)	44% (37–51)	69% (64–74)	74% (65–81)
T2 + DWI + DCE	88% (84–92)	44% (37–51)	69% (64–74)	72% (64–80)
Dominant pattern 4: Gleason score ≥4 + 3 irrespective of cancer core length				
T2	98% (90–100)	21% (17–25)	13% (10–17)	99% (94–100)
T2 + DWI	98% (90–100)	27% (23–31)	14% (11–18)	99% (95–100)
T2 + DWI + DCE	100% (93–100)	28% (24–32)	14% (11–18)	100% (97–100)
Any pattern 4: Gleason score ≥3 + 4 irrespective of cancer core length				
T2	93% (89–96)	34% (28–41)	64% (59–68)	79% (69–87)
T2 + DWI	89% (85–93)	42% (35–48)	66% (61–70)	76% (67–83)
T2 + DWI + DCE	89% (85–93)	43% (36–49)	66% (61–71)	76% (68–84)

DCE = dynamic contrast-enhanced imaging; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value.

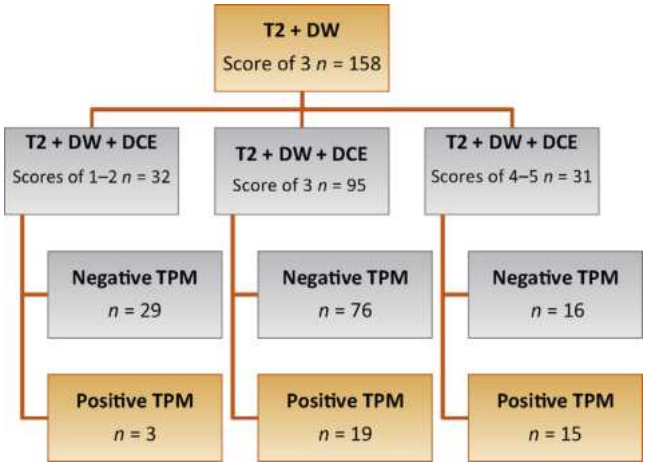


Fig. 2 – Flowchart describing changes to the scores of 3/5 on T2 + DWI that were made with the addition of contrast, and the results of TPM biopsy for UCH definition 1 disease. DCE = dynamic contrast-enhanced imaging; DWI = diffusion-weighted imaging; TPM = transperineal prostate mapping; UCH = University College Hospital.

When using an alternative threshold of histological significance (definition 2, any tumour of grade ≥3 + 4 and any tumour of grade ≥4 + 3), there were no statistically significant differences in diagnostic accuracy metrics between T2 + DWI and T2 + DWI + DCE (Table 4, $p > 0.05$ in all cases).

Addition of DCE was helpful in correctly identifying all 53 dominant pattern 4 lesions (Table 4) compared with both T2 and T2 + DWI, which assigned one case as nonsuspicious (a score of 2 compared with a score of 3 with DCE). Using DCE in combination with T2 + DWI, 25% (123/497) of patients were scored negative for a significant tumour on MRI, compared with 24% (121/497) with T2 + DWI alone ($p = 0.8$, McNemar's test). The addition of DCE reduced the number of equivocal scores (3/5) slightly, with 28% of patients classified as equivocal compared with 32% using T2 + DWI alone ($p = 0.031$, McNemar's test; Table 3). Fig. 2 outlines the changes to scores of 3/5 on T2 + DWI that were made with the addition of contrast, together with the corresponding histological results.

Figs. 3 and 4 show the proportion of significant tumours for each MRI score, using T2 + DWI and T2 + DWI + DCE, for four definitions of clinically significant cancer.

4. Discussion

4.1. Main findings

The addition of DCE to T2 and DWI did not improve diagnostic accuracy in a multicentre study that compared MRI with transperineal mapping biopsy as a reference standard for the detection of clinically significant prostate cancer. The proportion of patients with an equivocal score of 3 was slightly lower for DCE versus non-DCE reporting.

4.2. Previous publications

Three groups in particular have examined a strategy of limited "biparametric" MRI (T2 and DWI sequences) as a subset of full PIRADS 2–compliant MP-MRI [13–15]. The methods vary widely, with a DCE time resolution between 3 s [14] and 8 s [13], and template saturation biopsy [13], targeted biopsy [14], or TRUS biopsy and prostatectomy [15] for histological confirmation, as well as differences in reader experience and reporting criteria. None, however, found a significant improvement in diagnostic accuracy with contrast. The heterogeneity in methods suggests that a meta-analysis will be challenging, although it has been attempted: Woo et al [16] found 20 studies suitable for inclusion in a meta-analysis of "head–to-head" comparisons, with a total of 2142 patients. They found no convincing difference between biparametric MRI and MP-MRI with contrast, although they acknowledged (and attempted to analyse) differences in MRI field strength, use of endorectal coil, reader experience, reporting system (Likert/PIRADS 1/PIRADS 2), use of DCE parametric analysis, and DCE time resolution.

We found that sensitivity of T2 sequences alone for significant tumours was high. It has been known for some time that most significant prostate cancers are visible on T2 sequences, in both the peripheral [17] and the transition

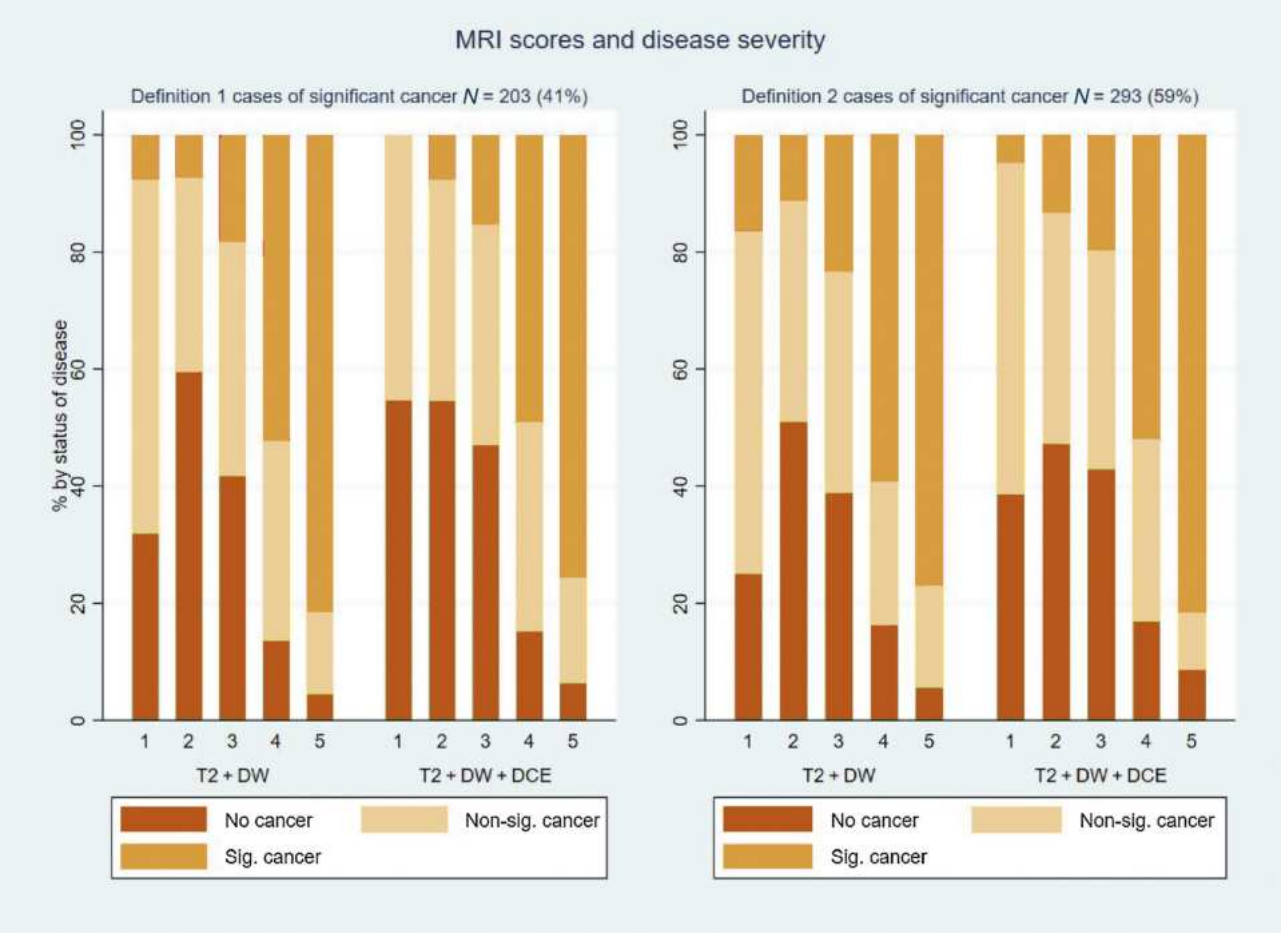


Fig. 3 – Distribution of MRI scores and their correlated histological results: definitions 1 and 2. DCE = dynamic contrast-enhanced imaging; DW = diffusion weighted; MRI = magnetic resonance imaging; Sig. = significant.

zone [18], but in both previous studies and the current one, it was at the expense of low specificity and a high proportion of equivocal (3/5) scores. As few centres perform T2 imaging alone, we did not include these results in statistical comparisons.

4.3. *Methodological limitations*

A number of aspects of the PROMIS study make it particularly relevant to a group of men undergoing MRI as a triage test before biopsy [19]. First, all men with a suspicion of tumour and PSA < 15 were included, with only a small number of exclusions due to difficulty performing the biopsy or T4 status.

In addition, the reference standard of transperineal mapping biopsy was applied to all patients without knowledge of the MRI result. This prevents the biases inherent in using MRI-targeted biopsy for confirmation, particularly for a study assessing validity. The study was multicentre and used local radiologists of varying experience for the primary analysis. The protocol was applicable widely, using 1.5 T magnets, no endorectal coil, and a feasible DCE time resolution of 15 s.

However, there are also potential limitations. First, the analysis was at the level of the prostate: no attempt was made to correlate the position of the tumour on the MRI and TPM biopsy. This has important implications when making inferences about biopsy strategy, but is not relevant when assessing our performance in identifying men at a low risk of significant tumours (in other words, in identifying prostates negative for significant cancer). Second, we used a Likert reporting system, which could limit the direct applicability of the study to PIRADS 2–based reporting. However, it may also have helped detect any potential advantages of DCE, because it allowed the enhanced images (including any morphological criteria that the radiologist deemed useful) to influence the overall suspicion of tumour, rather than just distinguishing between PIRADS 3 and 4 lesions as in the current PIRADS 2 reporting framework [3]. A Likert reporting system has also been recommended for use in the UK by consensus panels [20] and recent National Institute for Health and Care Excellence guidance in the UK [1]. Third, the DCE sequences were biased towards anatomical resolution rather than time resolution, improving image quality but potentially excluding calculation of parameters such as K-trans. However, recent PIRADS 2.1 guidelines acknowledge the lack of data to support a high temporal resolution [4], and PIRADS 2 does not include a recommendation for routine parametric analysis because of a continuing lack of data showing its benefits over

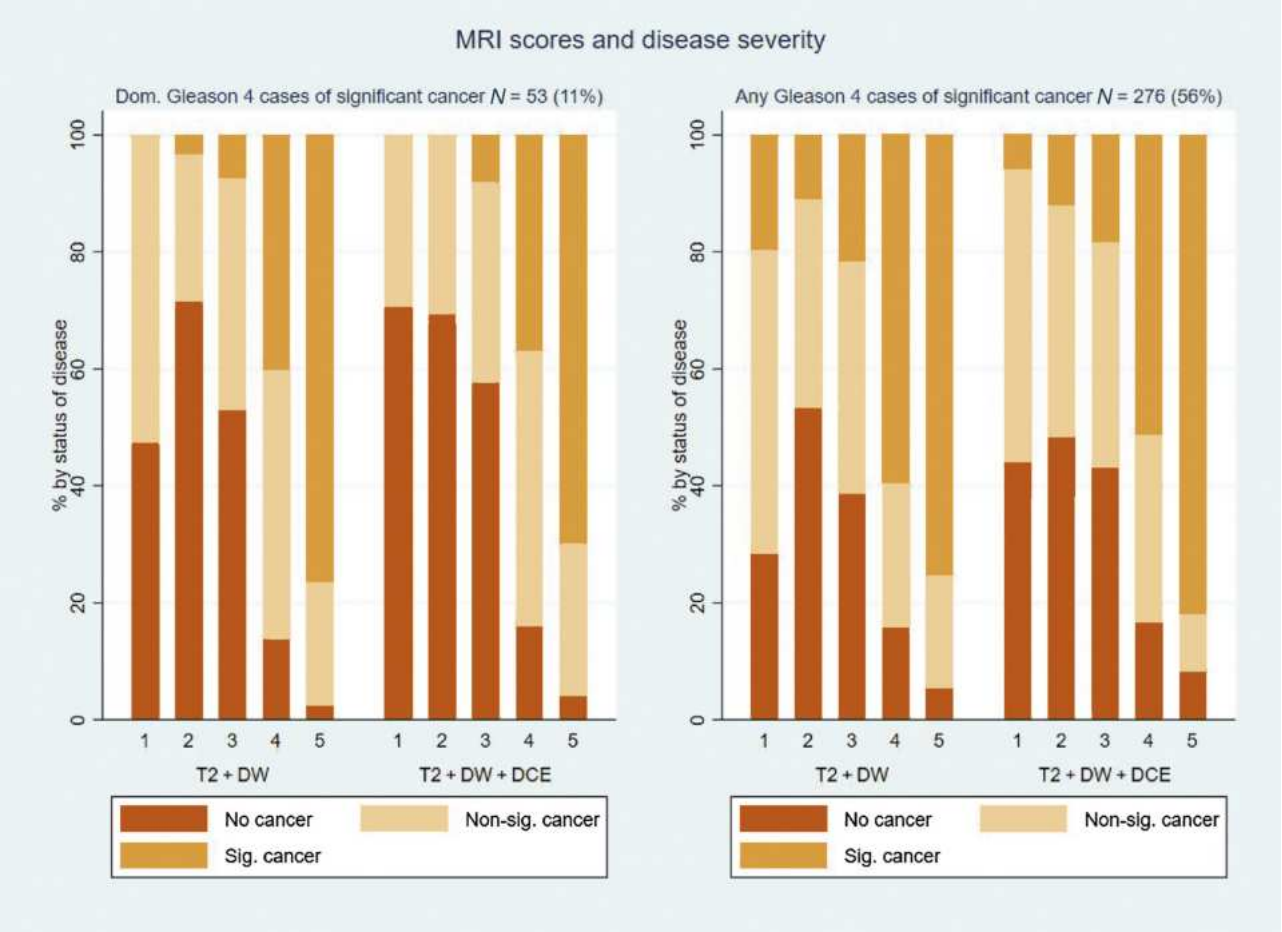


Fig. 4 – Distribution of MRI scores and their correlated histological results: Gleason dominant 4 or higher, and any Gleason 4 or higher. DCE = dynamic contrast-enhanced imaging; Dom. = dominant; DW = diffusion weighted; MRI = magnetic resonance imaging; Sig. = significant.

interpreting the early enhanced images [3]. Fourth, the PROMIS study was conducted using 1.5 T machines, and it is possible that the benefits of dynamic sequences are accentuated with a higher magnetic field strength or the use of an endorectal coil, although two recent studies performed at 3 T suggest otherwise [13,14]. Fifth, the radiologist was allowed to know the PSA during reporting. Especially with the potentially subjective analysis of Likert scoring, this information (rather than MRI criteria alone) may have influenced the overall score, in particular inclining the reporter away from a potential "miss" in the case of a high PSA density. Thus, while knowing the PSA reflects real-world practice, it may result in an overestimate of the performance of MRI, whatever the protocol. Finally, the reporting was not supervised, so we cannot absolutely rule out some reporters not looking at and reporting the sequences in the correct order. The importance of doing so was, however, emphasised in written and oral training material. The method of reporting in one sitting enabled a truly prospective study, but we cannot eliminate a possible bias from the reporters knowing, when they reported the T2 and diffusion sequence, that there was a "final" score using contrast that would be used for the main outcome of the study.

4.4. *Application to clinical practice*

While the PROMIS study demonstrates the diagnostic accuracy of biparametric MRI as a triage test for safely avoiding biopsy, it does not address some important potential benefits of using contrast. There is some evidence that dynamic contrast-enhanced images improve the measurement of tumour volume [21], although this result is not replicated by all [22]. If true, this may well be because the margins of some tumours are well delineated with contrast and it is possible that it may improve the conduct of targeted biopsies, although no study has attempted to quantify the effect. In addition, there is some evidence that DCE sequences may improve planning for focal therapy [22] or staging tumour at the capsule [23–25]. Finally, there is a consensus that DCE is useful after radiotherapy or ablation [26,27], although the size of the effect when high-quality DWI is used has been questioned [28,29]. These potential benefits of contrast must be weighed against its expense and potential risk [30].

Most of the studies on the value of contrast have used experienced readers, but there is some evidence that it helps those with less experience: in a study of 68 selected patients, DCE increased significantly the performance of

radiologists with either 100 or 300 cases of reporting experience, but not in those with 1000 cases [31]. This patient group was biased, but even if the result holds in subsequent studies, it is a matter of debate whether a sensible approach is the routine use of contrast, or improved mentorship, specialisation, and second reads in difficult cases. Similarly, the PIRADS 2.1 document discusses the utility of contrast as a "safety net" in difficult cases, where the other sequences are of suboptimal quality; it is a matter of debate whether this is routinely included in a scan protocol or used (perhaps in a structure that allows recalls for suboptimal scans) where it is needed.

Finally, the finding that a lower proportion of patients were given equivocal scores of 3 when contrast was used was statistically significant. However, any clinical impact depends on the way equivocal cases are managed—in particular, whether they undergo biopsy or close surveillance [18].

5. Conclusions

The addition of dynamic contrast enhancement did not significantly improve the diagnostic accuracy of T2 + diffusion MRI in a multicentre, multireader study using 1.5 T scans. The findings are consistent with recent data from other groups and allow us to question the necessity of the routine use of contrast in a prebiopsy triage setting, if high-quality MRI is reported by experienced readers.

***Author contributions*:** Ahmed El-Shater Bosaily had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: El-Shater Bosaily, Ahmed, Emberton, Kaplan, Brown, Freeman, Jameson, Kirkham.
Acquisition of data: All authors.
Analysis and interpretation of data: El-Shater Bosaily, Ahmed, Emberton, Kaplan, Brown, Freeman, Jameson, Kirkham, Frangou.
Drafting of the manuscript: El-Shater Bosaily, Ahmed, Emberton, Kaplan, Brown, Kirkham, Frangou.
Critical revision of the manuscript for important intellectual content: El-Shater Bosaily, Ahmed, Emberton, Kaplan, Brown, Kirkham, Frangou.
Statistical analysis: El-Shater Bosaily, Ahmed, Emberton, Kaplan, Brown, Kirkham, Frangou.
Obtaining funding: Ahmed, Emberton.
Administrative, technical, or material support: Brown, Frangou.
Supervision: None.
Other: This work reports on a multicentre national trial. All authors have contributed to the conduct of the trial in their prospective centres.

Financial disclosures: Ahmed El-Shater Bosaily certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** We acknowledge funding from the National Institute of Health Research (NIHR) Health Technology Assessment and Prostate Cancer UK (project number 09/22/67). This project is also supported and partially funded by UCLH/UCL Biomedical Research Centre and the Royal Marsden and Institute for Cancer Research Biomedical Research Centre, and is coordinated by the Medical Research Council Clinical Trials Unit (MRC CTU) at UCL. It is sponsored by University College London (UCL). MRC CTU at UCL is supported by an MRC Core grant (MC_UU_12023/28). Mark Emberton's and Alex Kirkham's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. Hashim Ahmed receives funding from the Medical Research Council (UK). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the health technology assessment program, NIHR, NHS, or the Department of Health.

References

[1] NICE. NICE guidance—prostate cancer: diagnosis and management. BJU Int 2019;124:9–26.
[2] Barentsz JO, et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012;22:746–57.
[3] Weinreb JC, et al. PI-RADS Prostate Imaging—Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40.
[4] Turkbey B, et al. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate Imaging Reporting and Data System version 2. Eur Urol 2019;76:340–51.
[5] Ahmed HU, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[6] Bossuyt PM, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Radiology 2015;277:826–32.
[7] El-Shater Bosaily A, et al. PROMIS—prostate MR imaging study: a paired validating cohort study evaluating the role of multi-parametric MRI in men with clinical suspicion of prostate cancer. Contemp Clin Trials 2015;42:26–40.
[8] Brown LC, et al. Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study. Health Technol Assess 2018;22:1–176.
[9] Likert R. A technique for the measurement of attitudes. Arch Psychol 1932;22:1–55.
[10] Ahmed HU, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol 2011;186:458–64.
[11] Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. Biometrics 2000;56:345–51.
[12] Wang W, Davis CS, Soong S-J. Comparison of predictive values of two diagnostic tests from the same sample of subjects using weighted least squares. Stat Med 2006;25:2215–29.
[13] Barth BK, et al. Detection of clinically significant prostate cancer: short dual–pulse sequence versus standard multiparametric MR imaging—a multireader study. Radiology 2017;284:725–36.
[14] Kuhl CK, et al. Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen. Radiology 2017;285:493–505.
[15] Junker D, et al. Comparison of multiparametric and biparametric MRI of the prostate: are gadolinium-based contrast agents needed for routine examinations? World J Urol 2018;37:691–9.
[16] Woo S, et al. Head-to-head comparison between biparametric and multiparametric MRI for the diagnosis of prostate cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 2018;211:W226–41.
[17] Hricak H, et al. Carcinoma of the prostate gland: MR imaging with pelvic phased-array coils versus integrated endorectal-pelvic phased-array coils. Radiology 1994;193:703–9.
[18] Akin O, et al. Transition zone prostate cancers: features, detection, localization, and staging at endorectal MR imaging. Radiology 2006;239:784–92.
[19] Ahmed HU, et al. Is it time to consider a role for MRI before prostate biopsy? Nat Rev Clin Oncol 2009;6:197–206.

[20] Brizmohun Appayya M, et al. National implementation of multiparametric magnetic resonance imaging for prostate cancer detection—recommendations from a UK consensus meeting. BJU Int 2018;122:13–25.
[21] Sun C, et al. Comparison of T2-weighted imaging, DWI, and dynamic contrast-enhanced MRI for calculation of prostate cancer index lesion volume: correlation with whole-mount pathology. AJR Am J Roentgenol 2019;212:351–6.
[22] Cornud F, et al. Tumor target volume for focal therapy of prostate cancer-does multiparametric magnetic resonance imaging allow for a reliable estimation? J Urol 2014;191:1272–9.
[23] Bloch BN, et al. Prediction of prostate cancer extracapsular extension with high spatial resolution dynamic contrast-enhanced 3-T MRI. Eur Radiol 2012;22:2201–10.
[24] Fütterer JJ, et al. Staging prostate cancer with dynamic contrast-enhanced endorectal MR imaging prior to radical prostatectomy: experienced versus less experienced readers. Radiology 2005;237:541–9.
[25] Puech P, Sufana-Iancu A, Renard B, Lemaitre L. Prostate MRI: can we do without DCE sequences in 2013? Diagn Interv Imaging 2013;94:1299–311.
[26] Turkbey B, et al. Correlation of magnetic resonance imaging tumor volume with histopathology. J Urol 2012;188:1157–63.
[27] Mason J, Adiotomre E, Bownes P, Carey B, Henry A. Importance of dynamic contrast enhanced magnetic resonance imaging for targeting biopsy and salvage treatments after prostate cancer recurrence. J Contemp Brachythер 2018;10:570–2.
[28] Lotte R, et al. Multiparametric MRI for suspected recurrent prostate cancer after HIFU: is DCE still needed? Eur Radiol 2018;28:3760–9.
[29] Luzurier A, et al. Dynamic contrast-enhanced imaging in localizing local recurrence of prostate cancer after radiotherapy: limited added value for readers of varying level of experience. J Magn Reson Imaging 2018;48:1012–23.
[30] Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ. Gadolinium-based contrast agents: a comprehensive risk assessment. J Magn Reson Imaging 2017;46:338–53.
[31] Gatti M, et al. Prostate cancer detection with biparametric magnetic resonance imaging (bpMRI) by readers with different experience: performance and comparison with multiparametric (mpMRI). Abdom Radiol 2019;44:1883–93.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 503–511 of this issue

Can Biparametric Prostate Magnetic Resonance Imaging Fulfill its PROMIS?

Maarten de Rooij [a], *Bas Israël* [a,b], *Joyce G.R. Bomers* [a], *Ivo G. Schoots* [c,d], *Jelle O. Barentsz* [a,*]

[a] *Department of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands;* [b] *Department of Urology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands;* [c] *Department of Radiology, Nuclear Medicine and Anatomy, Erasmus University Medical Center, Rotterdam, The Netherlands;* [d] *Department of Radiology, Netherlands Cancer Institute, Amsterdam, The Netherlands*

Recently updated international guidelines recommend a more prominent role for multiparametric magnetic resonance imaging (mpMRI) in the work-up for prostate cancer (PCa) diagnosis [1,2]. However, the benefit of dynamic contrast-enhanced (DCE) MRI for PCa detection and localization is still a matter of debate. Omitting DCE may improve MRI accessibility in response to the increasing demand for this imaging modality. A so-called biparametric MRI (bpMRI) protocol only uses T2-weighted and diffusion-weighted imaging. There are several advantages of using a bpMRI strategy for all biopsy-naïve patients, the most enticing one being time and costs savings [3–5]. Furthermore, the potential side effects of contrast can be avoided [6].

Recent systematic reviews and meta-analyses found similar diagnostic performance for bpMRI and mpMRI, suggesting a transition to bpMRI for biopsy-naïve men could be feasible [7,8]. However, the studies included showed high methodologic heterogeneity in prior biopsy status, MRI equipment, MRI protocol and scoring system, the definition of clinically significant cancer, and (biopsy) reference standard. This undermines the strength of the underlying evidence. Furthermore, the studies included were often from highly experienced prostate centers with 3-T equipment, which somewhat limits the generalizability of these data to general clinical practice [5].

We commend El-Shater Bosaily et al [9] on their study published in this issue of *European Urology*, as it contributes to filling this void in the literature. For the original PROMIS study the intent was to reflect "daily clinical practice" with 1.5-T MRI scanners and multiple readers with varying prostate MRI reading experience [10]. As an additional aim, the value of mpMRI over bpMRI was assessed within the setting of this prospective, multicenter, multireader and paired validation study with template mapping (TMP) biopsies as the reference standard. The diagnostic performance of both techniques in detecting clinically significant disease in 497 biopsy-naïve men was compared using a 5-point Likert scoring system. The authors conclude that the diagnostic accuracy values for mpMRI and bpMRI are similar, suggesting that DCE could be omitted from the MRI diagnostic work-up.

Some issues in the present study by El-Shater Bosaily and colleagues should be critically appraised. First, it is important to realize that the conclusions from this PROMIS study are based on the assumption that targeted biopsies (which were not performed in this study) would achieve similar diagnostic accuracy as TMP biopsy. What is currently lacking, however, is an assessment of the correlation between lesion location on MRI and TMP biopsy to be able to justify the assumption made.

Second, the PROMIS data show a clear difference in the total number of "equivocal" or "uncertain" cases (ie, Likert score of 3 out of 5) for bpMRI and mpMRI (32% vs 27%) compared to studies by Van der Leest et al (the 4M study; 7.8% vs 6.4%) [5] and Zawaideh et al (17% vs 8.3%) [11]. The low percentage of equivocal results in the latter two studies can be explained by the high-quality 3-T images assessed by experienced readers, whereas images from routine 1.5-T scanners were read by radiologists with varying experience

DOI of original article: https://doi.org/10.1016/j.eururo.2020.03.002.
* Corresponding author. Department of Radiology, Radboud University Nijmegen Medical Center, P.O. Box 9101, Nijmegen, The Netherlands. Tel. +31 24 3619196.
E-mail address: jelle.barentsz@radboudumc.nl (J.O. Barentsz).

https://doi.org/10.1016/j.eururo.2020.04.062

levels in the PROMIS study. Despite the high number of equivocal cases in the PROMIS study, the reduction in "uncertainty" by using DCE (mpMRI) was only 4.4% (31.8% to 27.4%), while Zawaideh et al reported substantially greater of 8.7% (17% to 8.3%) [11]. Moreover, the suboptimal "blinding" protocol used in the PROMIS study for the bpMRI and mpMRI readings may have resulted in a significant bias.

It is apparent that omitting DCE from prostate MRI would allow a higher throughput and lower costs, would make prostate MRI noninvasive, and would avoid potential contrast-related side-effects. However, suboptimal results because of lower image quality from the use of suboptimal MRI scanners and less experienced radiologists could be mitigated by the use of DCE in mpMRI protocols to decrease uncertainty (ie, decrease scores of 3). Equivocal MRI scores are troublesome for urologists, as they do not give guidance in biopsy decision-making. High numbers of equivocal cases could result in a loss of confidence in the MRI pathway and prompt urologists to lean back towards the systematic biopsy pathway. Previous studies reported that DCE could aid in assessment and decrease uncertainty in reading, especially in settings with suboptimal image quality and non-expert readers [12,13]. Therefore, focusing on high-quality examinations and adequate training for radiologists is crucial.

Thus, before using bpMRI routinely, radiologists should be competent in both bpMRI and mpMRI. In daily practice, we see many radiologists performing bpMRI who are "unaware-incompetent" in this respect. Ideally, prostate MRI radiologists should compare their bpMRI and mpMRI diagnosis with histopathologic outcomes and attend multidisciplinary team meetings to this end. In addition, reading performance should be benchmarked against results from expert centers and the literature. Only if these conditions are fulfilled, we agree with El-Shater Bosaily et al that there is a role for bpMRI as a triage test for the detection of clinically significant PCa, but only in men in whom biopsy avoidance is a clinical priority, such as in early detection of cancer in biopsy-naïve men with a lower risk of clinically significant PCa. For men with high clinical suspicion for significant disease, for whom the clinical priority is cancer detection and not biopsy avoidance, mpMRI is preferred over bpMRI.

We conclude with some points on the use of bpMRI in daily practice that should be considered:

- Only perform bpMRI when image quality and radiological readings are of a high standard.
- Use high-quality bpMRI only for men for whom biopsy avoidance is a clinical priority, such as for early cancer detection in biopsy-naïve men with a lower risk of clinically significant PCa.
- Perform mpMRI as the default for men with a high clinical suspicion for significant disease, where the priority is cancer detection and not biopsy avoidance. Perform mpMRI for men with persisting clinical suspicion after a previous negative biopsy (Fig. 1) or previous negative

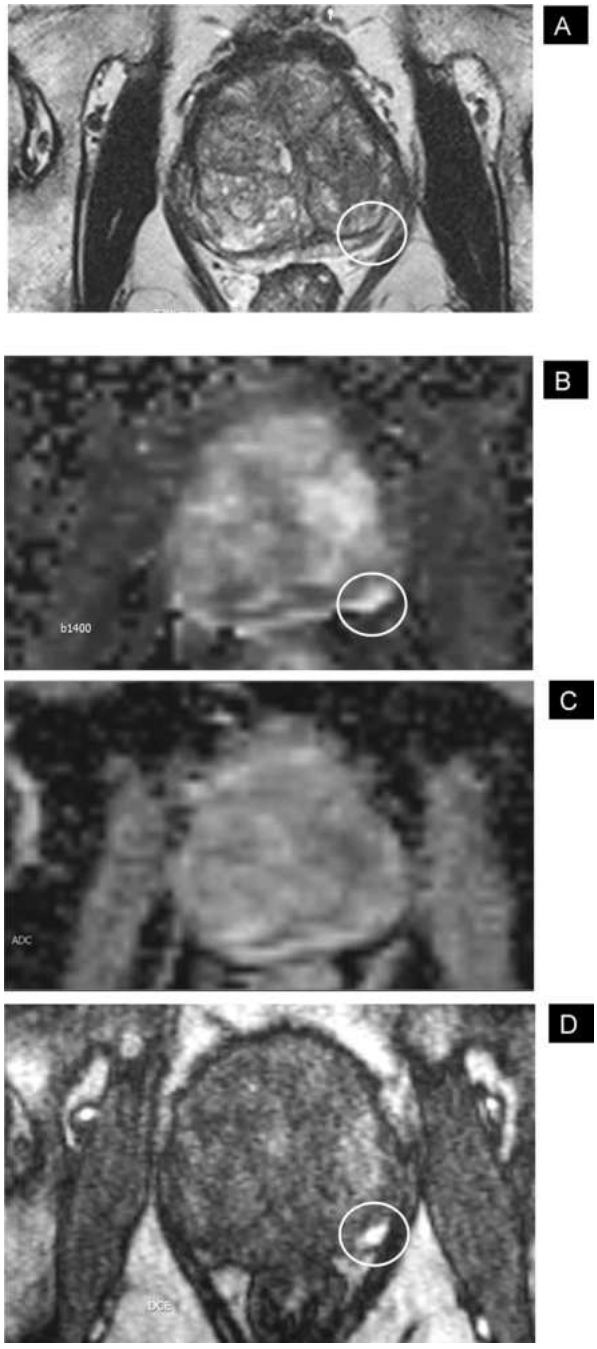


Fig. 1 – High-grade prostate cancer missed on bpMRI. The patient was 74 yr old with prostate-specific antigen of 9.6 ng/mL. Digital rectal examination revealed T0 and the patient had one negative systematic transrectal ultrasound–guided biopsy. bpMRI, consisting of (A) axial T2W, (B) axial DWI b1400, and (C) axial ADC images revealed prospectively no suspicious lesions, only small geographic abnormalities. A PI-RADS score of 2 (T2W/DWI/DCE: 2/2/X) was assigned to the prostate. However, on the (D) "early" DCE image, focal enhancement was identified in the peripheral zone at the 5-o'clock position in the mid-prostate (circle). This focal enhancement was then correlated to focal (A) low T2W and (B) minimal high b1400 signal intensity (circles). The final assessment was PI-RADS 4 (T2W/DWI/DCE: 4/3/+ and upgraded to final score of 4). Transperineal MRI-guided biopsy showed an ISUP grade 4 cancer (Gleason score 4 + 4 = 8). The patient had a successful radical prostatectomy (pT2N0R0, ISUP grade 4). bpMRI = biparametric magnetic resonance imaging; T2W = T2-weighted imaging; DWI = diffusion-weighted imaging; ADC = apparent diffusion coefficient; PI-RADS = Prostate Imaging-Reporting and Data System; DCE = dynamic contrast enhancement; ISUP = International Society of Urological Pathology.

bpMRI, for men with previous prostate treatment, and for men suspected to have cancer recurrence.

This critically appraised PROMIS study represents a great effort. However, additional prospective, randomized or head-to-head multicenter studies using multiple readers and addressing the noninferiority of biopsy yields of MRI-directed biopsies prompted by bpMRI and mpMRI approaches are needed, to confidently recommend bpMRI as the default in PCa diagnosis.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Bjurlin MA, Carroll PR, Eggener S, et al. Update of the standard operating procedure on the use of multiparametric magnetic resonance imaging for the diagnosis, staging and management of prostate cancer. J Urol 2020;203:706–12. http://dx.doi.org/10.1097/JU.0000000000000617.

[2] Mottet N, van den Bergh RCN, Briers E, et al. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer 2019. Arnhem: The Netherlands: European Association of Urology; 2019.

[3] Porter KK, King A, Galgano SJ, Sherrer RL, Gordetsky JB, Rais-Bahrami S. Financial implications of biparametric prostate MRI. Prostate Cancer Prostat Dis 2020;23:88–93.

[4] Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V. Cost-effectiveness of MR imaging-guided strategies for detection of prostate cancer in biopsy-naive men. Radiology 2017;285:157–66.

[5] van der Leest M, Israël B, Cornel EB, et al. High diagnostic performance of short magnetic resonance imaging protocols for prostate cancer detection in biopsy-naive men: the next step in magnetic resonance imaging accessibility. Eur Urol 2019;76:574–81.

[6] Schieda N, Krishna S, Davenport MS. Update on gadolinium-based contrast agent-enhanced imaging in the genitourinary system. Am J Roentgenol 2019;212:1223–33.

[7] Alabousi M, Salameh JP, Gusenbauer K, et al. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naive patients: a diagnostic test accuracy systematic review and meta-analysis. BJU Int 2019;124:209–20.

[8] Kang Z, Min X, Weinreb J, Li Q, Feng Z, Wang L. Abbreviated biparametric versus standard multiparametric MRI for diagnosis of prostate cancer: a systematic review and meta-analysis. Am J Roentgenol 2019;212:357–65.

[9] El-Shater Bosaily E, Frangou E, Ahmed HU, et al. Additional value of dynamic contrast-enhanced sequences in multiparametric prostate magnetic resonance imaging: data from the PROMIS study. Eur Urol 2020;78:503–11.

[10] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.

[11] Zawaideh JP, Sala E, Shaida N, et al. Diagnostic accuracy of biparametric versus multiparametric prostate MRI: assessment of contrast benefit in clinical practice. Eur Radiol. In press. https://doi.org/10.1007/s00330-020-06782-0.

[12] Gatti M, Faletti R, Calleris G, et al. Prostate cancer detection with biparametric magnetic resonance imaging (bpMRI) by readers with different experience: performance and comparison with multiparametric (mpMRI). Abdom Radiol 2019;44:1883–93.

[13] Greer MD, Brown AM, Shih JH, et al. Accuracy and agreement of PIRADSv2 for prostate cancer mpMRI: a multireader study. J Magn Reson Imaging 2017;45:579–85.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority Brief Correspondence

Editorial by James Thompson, Amer Amin and Phillip Stricker on pp. 518–519 of this issue

Multiparametric Magnetic Resonance Imaging Alone is Insufficient to Detect Grade Reclassification in Active Surveillance for Prostate Cancer

Carissa E. Chu [a], *Peter E Lonergan* [a], *Samuel L. Washington* [a], *Janet E Cowan* [a], *Katsuto Shinohara* [a], *Antonio C. Westphalen* [a,b], *Peter R. Carroll* [a], *Matthew R Cooperberg* [a,c,*]

[a] *Department of Urology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA;* [b] *Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA;* [c] *Department of Epidemiology & Biostatistics, University of California, San Francisco, CA, USA*

Article info

Article history:
Accepted June 10, 2020

Associate Editor:
James Catto

Statistical Editor:
Melissa Assel

Keywords:
Prostate cancer
Active surveillance
Multiparametric magnetic resonance imaging
Biopsy
Upgrade

Abstract

Multiparametric magnetic resonance imaging (mpMRI) has improved the detection of clinically significant prostate cancer. It remains unclear, however, whether mpMRI can safely replace confirmatory or surveillance biopsies in men with low-risk disease managed with active surveillance (AS). Overall, 166 men were upgraded at a median of 29 mo (interquartile range 13–54). The overall negative predictive value (NPV) of mpMRI was 79.5% and ranged from 74.4% to 84.6% for all AS biopsies up to the fourth surveillance biopsy. In men with prostate-specific antigen density $\geq$0.15 ng/ml/cm^3, the overall NPV of mpMRI was 65.5% and ranged from 57.1% to 73.3% across serial mpMRI scans. These findings support the hypothesis that mpMRI is helpful but insufficient to rule out pathological reclassification, especially at confirmatory biopsy or in the presence of other risk factors.

Patient summary: Multiparametric magnetic resonance imaging (mpMRI) alone misses a considerable percentage of clinically significant prostate cancers (Gleason grade group $\geq$2) in men on active surveillance for low-risk prostate cancer. We conclude that mpMRI alone cannot safely replace surveillance prostate biopsies, particularly at confirmatory biopsy or in the presence of other risk factors.

* Corresponding author at:Department of Urology, University of California, 550 16th Street, San Francisco, CA 94143, USA.
E-mail address: matthew.cooperberg@ucsf.edu (M.R. Cooperberg).

For men with low-risk prostate cancer, active surveillance (AS) is recommended to avoid the side effects of immediate treatment and identify those who would eventually benefit from definitive intervention [1,2]. Multiparametric magnetic resonance imaging (mpMRI) of the prostate is increasingly used to diagnose, stage, and risk-stratify prostate cancer, although its long-term benefits remain investigational [2]. National guidelines support the optional use of mpMRI in determining suitability for AS [2]. It is unknown, however, whether a negative mpMRI scan can obviate the need for a confirmatory biopsy or any biopsies thereafter. Reducing the frequency of surveillance biopsy could mitigate risks of hemorrhage- and sepsis-related complications in selected men at low risk of disease reclassification.

Pooled negative predictive values (NPVs) for mpMRI range from 88% to 93% [3] for clinically significant cancer on

https://doi.org/10.1016/j.eururo.2020.06.030
0302-2838/

diagnostic systematic biopsies, to as low as 72% on whole-mount prostatectomy specimens [4]. Collectively, these studies raise concerns about replacing systematic biopsies with mpMRI when no lesion is seen [5]. In a recent study of 207 men on AS, the NPV of mpMRI was 85% at 3-year systematic surveillance biopsy [6]. However, the NPV of mpMRI more generally in AS is unknown. In this study, we determined the NPV of prostate mpMRI in the detection of Gleason grade group (GG) ≥2 disease on confirmatory and multiple surveillance biopsies among men on AS initially diagnosed with GG 1 prostate cancer.

This was a single-center study of men prospectively enrolled on AS from 2001 to 2017 who provided informed consent under local institutional review board supervision. Men were diagnosed with GG 1 prostate via systematic biopsy, followed by mpMRI before subsequent biopsies for up to four biopsies in total. Men who underwent MRI-fusion biopsy at diagnosis were excluded. Diagnostic biopsies performed elsewhere were re-reviewed by a genitourinary pathologist. The AS protocol included prostate-specific antigen (PSA) testing and digital rectal examination every 6 months, mpMRI every 12–18 months, and a surveillance biopsy every 1–2 years.

The mpMRI sequences included T2-weighted, dynamic contrast–enhanced, and diffusion weighted imaging (Supplementary Material). mpMRI scans were reviewed by a dedicated genitourinary radiologist (ACW) who also re-scored mpMRI scans performed before 2014 using Prostate Imaging-Data and Reporting System (PI-RADS) version 2. Negative mpMRI was defined as a PI-RADS score of 1–2. The PI-RADS version 2 score was determined for the most suspicious lesion if multiple lesions were present [7].

All biopsies were transrectal. Visible lesions were targeted using the UroNav system or cognitive fusion. Systematic 14-core biopsies of the medial and lateral aspects of each sextant and anterior prostate were also taken. If no visible lesion was seen on MRI, systematic biopsy alone was performed. The primary outcome was biopsy upgrading to GG ≥ 2. Each MRI scan was matched to its subsequent biopsy, and test characteristics were calculated on a per examination basis.

Overall, 344 men had at least one mpMRI scan and biopsy after diagnosis (Table 1). In total, 408 mpMRI scans were performed with a median of 16.5 mo (interquartile range [IQR] 13.0–24.0) between biopsies. The median time spent on AS was 71.0 months (IQR 51.5–92.5). 42 men (12.0%) had at least one negative biopsy before diagnosis. A median of 15 cores (IQR 12–18) were taken at diagnostic biopsy, with two cores (IQR 1–3) positive. Overall, 166 men were upgraded at a median of 29 months (IQR 13–54) on AS: 125 men (75.3%) were upgraded to GG 2, 30 (18.1%) to GG 3, 5 (3.0%) to GG 4, and 6 (3.6%) to GG 5. The cumulative incidence of upgrading was 22.0% at 2 years, 32.0% at 3 years, and 52.0% at 5 years.

At confirmatory (second) biopsy, the NPV of mpMRI was 74.4% and the sensitivity was 85.1%. For subsequent surveillance biopsies up to the fourth biopsy, the NPV was 84.6% and sensitivity was 92.9%. The overall NPV was 79.5% and sensitivity was 89.5%. For men with PSA density (PSAD) ≥0.15 ng/ml/cm^3, the NPV was 57.1% on confirmatory biopsy and 73.3% for subsequent surveillance biopsies up to the fourth biopsy; the overall NPV was 65.5% (Table 2). Conversely, for men with PSAD < 0.15 ng/ml/cm^3 the NPV was higher: 83.3% on confirmatory biopsy and 91.7% for subsequent surveillance biopsies up to the fourth biopsy; the overall NPV was 87.5% (Table 2). Among men with a history of negative biopsy before diagnosis, the overall NPV for biopsy upgrading was 93.3%. The upgrading distribution by PI-RADS score is shown in Supplementary Table 1. Clinical consequences of biopsies performed and avoided, and GG ≥ 2 prostate cancers diagnosed and missed, based on MRI alone with or without a PSAD cutoff of 0.15 ng/ml/cm^3, are summarized in Supplementary Table 2.

Table 1 – Patient characteristics at diagnosis for 344 men enrolled on active surveillance for prostate cancer at University of California, San Francisco.

Variable	Patients, *n* (%)
Age at diagnosis (yr)	
<60	120 (35)
60–69	187 (54)
≥70	37 (11)
Race/ethnicity	
Asian/Pacific Islander	18 (5)
Black/African American	10 (3)
White	264 (77)
Mixed/other/unknown	52 (15)
PSA at diagnosis (ng/ml)	
≤4	72 (21)
4.1–10	237 (69)
>10	34 (10)
CAPRA clinical risk	
Low (0–2)	292 (89)
Intermediate (3–5)	35 (11)
PI-RADS v2 score at confirmatory biopsy	
1	24 (14)
2	15 (9)
3	29 (16)
4	71 (40)
5	37 (21)
Location where magnetic resonance imaging was performed	
University of California, San Francisco	136 (96)
External institution	6 (4)

PI-RADS v2, Prostate Imaging-Reporting and Data System version 2; CAPRA, Cancer of the Prostate Risk Assessment; PSA, prostate specific antigen

In this study, 21.5% of men with GG 1 prostate cancer on AS and negative mpMRI were subsequently found to have GG ≥ 2 cancer, with an incidence of 14.3–25.6% per biopsy. These findings suggest that there is a persistent subset of men on AS with grade reclassification undetected by mpMRI. The NPV of mpMRI for biopsy upgrading was as low as 57.1% for men with PSAD ≥ 0.15 ng/ml/cm^3 (Table 2). By contrast, among patients with PSAD < 0.15 ng/ml/cm^3 and a prior confirmatory biopsy, negative mpMRI appears to be more reliably reassuring.

This is the first study reporting the NPV of mpMRI at multiple time points during AS. It supports previous findings that a percentage of clinically significant prostate cancers remain undetectable by mpMRI [6,8,9]. There are limitations to acknowledge. Two-thirds of diagnostic biopsies were performed at an external facility, and there was a high rate of biopsy upgrading in our cohort overall (52% at 5 years).

Table 2 – Characteristics of multiparametric magnetic resonance imaging for 344 men enrolled on active surveillance for prostate cancer at University of California, San Francisco.

	Magnetic resonance imaging after diagnostic biopsy								
	All patients ($n = 408$)			PSAD ≥ 0.15 ($n = 158$)			PSAD < 0.15 ($n = 245$)		
	CBx	SVBx	Overall	CBx	SVBx	Overall	CBx	SVBx	Overall
NPV (%)	74.4	84.6	79.5	57.1	73.3	65.5	83.3	91.7	87.5
PPV (%)	41.6	40.9	41.2	52.5	47.1	49.6	32.0	36.9	35.0
Sensitivity (%)	85.1	92.9	89.5	84.2	88.9	86.5	85.7	95.7	92.0
Specificity (%)	26.6	22.5	24.2	21.6	23.4	22.6	28.2	22.2	24.7

CBx = confirmatory biopsy; NPV = negative predictive value; PPV = positive predictive value; PSAD = prostate-specific antigen density (ng/ml/cm^3); SVBx = surveillance biopsy.

However, the cumulative incidence of upgrading—11% at 1 year, 22% at 2 years, and 32% at 3 years—is consistent with published rates of biopsy upgrading of 20–28% at 2–3 years [10,11]. In addition, our findings reflect the experience at an academic tertiary care center, which may limit the generalizability to other clinical practice settings.

In conclusion, mpMRI alone is insufficient to detect grade reclassification on AS, especially among men with PSAD ≥ 0.15 ng/ml/cm^3, and in particular should not replace confirmatory biopsy. As the precise role of mp-MRI in AS evolves, incorporating genomic biomarkers and other clinical parameters may improve diagnostic accuracy.

Author contributions: Carissa E. Chu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chu, Cooperberg
Acquisition of data: Cowan, Westphalen.
Analysis and interpretation of data: Chu, Lonergan, Washington, Cowan, Westphalen, Cooperberg, Carroll.
Drafting of the manuscript: Chu, Lonergan, Washington, Cowan, Cooperberg, Carroll.
Critical revision of the manuscript for important intellectual content: Chu, Washington, Lonergan, Cooperberg, Carroll.
Statistical analysis: Cowan.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Cooperberg.
Other: None.

Financial disclosures: Carissa E. Chu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.030.

References

[1] Bruinsma SM, Bangma CH, Carroll PR, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol 2016;13:151–67.
[2] Chen RC, Rumble RB, Loblaw DA, et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario guideline): American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2016;34:2182–90.
[3] Sathianathen NY, Omer A, Harriss E, et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer in the Prostate Imaging Reporting and Data System era: a systematic review and meta-analysis. Eur Urol 2020;78:402–14.
[4] Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol 2015;67:569–76.
[5] Marks LS. Some prostate cancers are invisible to magnetic resonance imaging! BJU Int 2016;118:492–3.
[6] Chesnut GT, Vertosick EA, Benfante N, et al. Role of changes in magnetic resonance imaging or clinical stage in evaluation of disease progression for men with prostate cancer on active surveillance. Eur Urol 2020;77:501–7.
[7] Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver reproducibility of the PI-RADS version 2 lexicon: a multicenter study of six experienced prostate radiologists. Radiology 2016;280:793–804.
[8] Amin A, Scheltema MA, Shnier R, et al. The MRI in Active Surveillance "MRIAS" trial: use of baseline mpMRI and saturation biopsy to reduce the frequency of surveillance prostate biopsies. J Urol 2020;203:910–7.
[9] Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917–28.
[10] Preston MA, Feldman AS, Coen JJ, et al. Active surveillance for low-risk prostate cancer: need for intervention and survival at 10 years. Urol Oncol 2015;33:383.e9–383.e16.
[11] Walton Diaz A, Shakir NA, George AK, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. Urol Oncol 2015;33:202.e1–e.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 515–517 of this issue.

Magnetic Resonance Imaging Improves Selection for Active Surveillance and Can Extend the Interval Between Biopsies

James Thompson [a,b,c,*], *Amer Amin* [a,b,c], *Phillip Stricker* [a,b]

[a] *St. Vincent's Prostate Cancer Centre, Sydney, Australia;* [b] *School of Medicine, University of New South Wales, Sydney, Australia;* [c] *Garvan Institute of Medical Research, Sydney, Australia*

Active surveillance (AS) evolved more than two decades ago as an active management strategy for low-risk prostate cancer to reduce overtreatment in response to evidence that many prostate cancers would cause no harm if left undetected. The PIVOT and ProtecT trials provided level 1 evidence that the risk of death at 10–15 yr is low even for watchful waiting without surveillance biopsy of International Society of Urological Pathology grade group 1–2 cancer [1,2].

Over the past decade, multiparametric magnetic resonance imaging (mpMRI) has emerged as the novel diagnostic test with highest incremental value to prostate-specific antigen (PSA) in selecting men for biopsy, superior to biomarkers in terms of ability to both predict significant cancer and precisely localise cancer within the gland, thus enabling targeted biopsy.

Prospective studies conducted by our group and the UK PROMIS/PRECISION study group [3–5] have provided the evidence base to justify routine mpMRI in men with raised PSA or abnormal digital rectal examination as a valid second-line screening tool, allowing biopsy to be deferred when normal, as endorsed by the 2020 European Association of Urology guidelines.

The widespread adoption of MRI in the diagnostic setting naturally led to the hypothesis that it may be useful in AS to reduce the frequency of surveillance biopsies and improve the sensitivity to detect significant cancer (when present) at surveillance biopsy.

We recently published our planned analysis of 3-yr biopsy outcomes for the first 100 men enrolled in the MRIAS trial [6]: this single-arm prospective study enrolled men suitable for AS following baseline transperineal saturation + MRI-ultrasound (US) fusion–targeted diagnostic biopsy, then followed them for 3 yr with annual surveillance MRI, PSA every 6 mo, and study endpoint biopsy at 3 yr. Confirmatory biopsy at 12 mo was removed from the surveillance protocol and instead only performed during the first 3 yr for predefined triggers, such as a new Prostate Imaging-Reporting and Data System (PI-RADS) 3–5 lesion, persistent PI-RADS 4–5 lesion, or rising PSA density/doubling time. The majority of men avoided biopsy before 3 yr, the progression rate was relatively low at 21%, the incidence of high-risk cancer missed by MRI was 1%, no patient experienced biochemical recurrence, and surveillance mpMRI had a negative predictive value (NPV) for significant cancer of 89%.

Our results are similar to a recent study by Dieffenbacher et al [7], whose nonrandomised comparative study revealed that baseline MRI/transrectal US (TRUS) fusion–targeted biopsy led to a much lower rate of progression on AS than 12-core transrectal biopsy without baseline MRI (19% vs 59%; $p < 0.001$). Together, these results suggest that baseline assessment with MRI-targeted + template sampling may be a safe alternative to the historical gold standard of 12–16-core TRUS biopsy at baseline and again within 12 mo.

In this issue of *European Urology*, Chu et al [8] report their retrospective analysis of 360 men who were initially diagnosed via median 14-core transrectal biopsy, with the major limitation of no MRI performed before diagnostic biopsy or at baseline selection for AS. Some 61% had a PI-RADS 4–5 lesion on initial MRI before confirmatory biopsy,

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.030.
* Corresponding author. St. Vincents Prostate Cancer Centre, 438 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. Tel. +61 2 80468050, Fax: +61 2 80468090.
E-mail addresses: drjethompson@gmail.com, j.thompson@unsw.edu.au (J. Thompson).

https://doi.org/10.1016/j.eururo.2020.07.001

and almost 50% (166/344) progressed to Gleason grade group 2, with a short median time to progression of only 29 mo, suggesting that for the majority the disease was misclassified due to sampling error at baseline rather than being due to true de novo grade progression.

They similarly found that if the MRI and confirmatory biopsy at 12 mo demonstrated no significant cancer and PSA density was <0.15, MRI had a high NPV of ~92% because of the low prevalence of subsequent progression. This is similar to the NPV of 89% for baseline MRI + transperineal biopsy reported in our MRIAS study, suggesting that their "double" biopsy (baseline + 12 mo) + MRI performed similarly to our MRIAS protocol.

Unfortunately, Chu et al do not provide detailed data on the cancers missed by MRI, but we can infer from the data reported that only 11/344 (3%) had Gleason grade group 4–5 tumours. The authors do not report the proportion of high-grade (Gleason grade group 4–5) tumours missed by MRI, but even if one-third of such tumours were missed (which is unlikely), this would equate to only 1% of the study population.

When interpreting studies of MRI in AS, the reader should consider three important observations:

1 The volume of high-grade tumour in cases missed by MRI is usually small; a 1–2-yr delay in detection and treatment of small-volume Gleason 7 tumours in <2–3% of an AS cohort by reducing the frequency of biopsy will rarely impact the likelihood of cure [1,2].
2 The role of interval changes over sequential MRI scans is important; in our study we observed that a PI-RADS 4 lesion that appeared de novo during AS or remained persistent over two interval MRI scans conferred a likelihood of >40% and >80%, respectively, of significant cancer. Conversely, if a baseline PI-RADS 4 lesion reverted to PI-RADS 2–3 after 12 mo on interval mpMRI, the likelihood of significant cancer was extremely low.
3 If MRI is incorporated into AS protocols to extend the interval between biopsies, men will still have interval template biopsies, but extending the interval may improve patient acceptability of and quality of life on AS and reduce the costs and risks of biopsy.

It is clear that MRI does miss the occasional high-grade cancer; however, novel imaging and biomarker tests may detect those MRI-invisible tumours. For example, we recently published the protocol for our multicentre prospective study of ^{68}Ga prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography + mpMRI before diagnostic biopsy [9]; preliminary analyses suggest that combining MRI and PSMA PET may incrementally improve both the NPV and positive predictive value for significant cancer. Perhaps MRI and PSMA PET will in future be alternated in AS protocols. Likewise, novel exosomal biomarkers in urine or blood show promise [10] and in combination with MRI could achieve a high enough NPV to justify deferring routine biopsy entirely. While we are discovering the ideal combination of tests and building an evidence base, there will continue to be a role for routine surveillance biopsy (perhaps at longer intervals) for at least the next decade.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377:132–42.
[2] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415–24.
[3] Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016;195:1428–35.
[4] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[5] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[6] Amin A, Scheltema MJ, Shnier R, et al. The Magnetic Resonance Imaging in Active Surveillance (MRIAS) trial: use of baseline multi-parametric magnetic resonance imaging and saturation biopsy to reduce the frequency of surveillance prostate biopsies. J Urol 2020;203:910–7.
[7] Dieffenbacher S., Nyarangi-Dix J., Giganti F., et al. Standardized magnetic resonance imaging reporting using the prostate cancer radiological estimation of change in sequential evaluation criteria and magnetic resonance imaging/transrectal ultrasound fusion with transperineal saturation biopsy to select men on active surveillance. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2019.03.001.
[8] Chu C, Lonergan P, Washington S, et al. Multiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer. Eur Urol 2020;78:515–7.
[9] Amin A, Blazevski A, Thompson J, et al. Protocol for the PRIMARY clinical trial, a prospective, multicentre, cross-sectional study of the additive diagnostic value of gallium-68 prostate-specific membrane antigen positron-emission tomography/computed tomography to multiparametric magnetic resonance imaging in the diagnostic setting for men being investigated for prostate cancer. BJU Int 2020;125:515–24.
[10] Klotz L, Tilki D, Fleshner N, DiRienzo A, Wang W, Tenniswood M. Analysis of small non-coding RNAs in urinary exosomes to classify prostate cancer into low-grade (GG1) and higher grade (GG2–5). J Clin Oncol 2020;38(6 Suppl):277.

EUROPEAN UROLOGY 78 (2020) 520–530

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer – Editor's Choice

Editorial by Ankeet Shah, Wei Phin Tan and Brant A. Inman on pp. 531–532 of this issue.

Enhanced Quality and Effectiveness of Transurethral Resection of Bladder Tumour in Non–muscle-invasive Bladder Cancer: A Multicentre Real-world Experience from Scotland's Quality Performance Indicators Programme

Paramananthan Mariappan [a,b,], Allan Johnston [c], Luisa Padovani [a], Eilidh Clark [b], Matthew Trail [d], Sami Hamid [d], Graham Hollins [e], Helen Simpson [f], Benjamin G. Thomas [a,g], Rami Hasan [e], Jaimin Bhatt [c], Imran Ahmad [c], Ghulam M. Nandwani [d], Ian D.C. Mitchell [f], David Hendry [c], for members of the Scottish Bladder Cancer QPI Research Collaborative*

[a] *Edinburgh Bladder Cancer Surgery, Department of Urology, Western General Hospital, Edinburgh, UK;* [b] *University of Edinburgh, Edinburgh, UK;* [c] *Department of Urology, Queen Elizabeth University Hospital, Glasgow, UK;* [d] *Department of Urology, Ninewells Hospital, Dundee, UK;* [e] *Department of Urology, University Hospital Ayr, Ayr, UK;* [f] *Department of Urology, Victoria Hospital, Kirkcaldy, UK;* [g] *Department of Urology, Borders General Hospital, Melrose, UK*

Article info

Article history:
Accepted June 22, 2020

Associate Editor:
James Catto

Keywords:
Bladder cancer
Non–muscle-invasive bladder cancer
Muscle-invasive bladder cancer
Quality indicators
Guidelines
Evidence-based medicine
Prognosis
Recurrence
Staging
Transurethral resection of bladder tumour

Abstract

Background: Clinical outcomes from non–muscle-invasive bladder cancer (NMIBC) are partly determined by the quality of initial interventions. To improve and standardise treatment for cancer, Scotland implemented a national Quality Performance Indicator (QPI) programme for bladder cancer (BC).
Objective: To evaluate compliance with specific quality indicators (QIs) related to transurethral resection of bladder tumour (TURBT) and to understand clinical outcomes from NMIBC following the introduction of the QPI programme.
Design, setting, and participants: Within a robust governance framework, 12 mandatory evidence-based QPIs were implemented nationally in April 2014. We report prospectively collected data for all new BC patients (between April 2014 and March 2017). We include follow-up data for 2689 patients.
Intervention: The TURBT-related QPIs were (1) using a bladder diagram, (2) single post-TURBT instillation of mitomycin C (SPI-MMC), (3) detrusor muscle (DM) in the specimen, and (4) early re-TURBT in high-risk NMIBC.
Outcome measurements and statistical analysis: We measured compliance with these QPIs and (1) recurrence rate at first follow-up cystoscopy (RRFFC), (2) rates of residual cancer, and (3) pT2 cancer at re-TURBT. Associations between QPI compliance, tumour features, and outcomes were assessed with multivariable logistic regression models.
Results and limitations: Among 4246 new BC patients, SPI-MMC was used in 67% (2029/3023) NMIBC patients. In 1860 NMIBC patients undergoing TURBT, RRFFC, rate of residual cancer, and rate of pT2 at re-TURBT were 13% (116/888), 33% (212/653), and 2.9% (19/653), respectively. SPI-MMC was associated with lower RRFFC, independent of all variables including hospital volume and surgeon. Presence of DM in the specimen

* Corresponding author. Department of Urology, Western General Hospital, University of Edinburgh, Crewe Road South, Edinburgh EH4 2XU, UK. Tel. +44 131 537 1000.
E-mail address: param.mariappan@nhs.net (P. Mariappan).

https://doi.org/10.1016/j.eururo.2020.06.051

halved the likelihood of residual disease in pT1 cancers. The main limitation is the lack of a pre-QPI introduction cohort for comparison.
Conclusions: The implementation of a QI programme in Scotland appears to facilitate high-quality TURBT, which in a real-world setting is associated with low early recurrence/residual cancer and accurate pathological staging.
Patient summary: Following the first 3 yr of implementing a novel Quality Performance Indicator (QPI) programme in Scotland, we assessed compliance and outcomes in non–muscle-invasive bladder cancer. Evaluating over 4000 new bladder cancer patients, we found that the QPI programme was associated with low recurrence and accurate staging following the initial transurethral resection of bladder tumour.

1. Introduction

Bladder cancer (BC) is a biologically heterogeneous malignancy, and the apparently modest improvement in survival over the past three decades or so, despite advances in treatment, is often attributed to this heterogeneity [1]. However, variation in clinical practice could also contribute to suboptimal outcomes [2]; despite strong evidence in favour of, for instance, neoadjuvant chemotherapy [3] and chemoradiotherapy [4], implementation is not ubiquitous. Likewise, in non–muscle-invasive bladder cancer (NMIBC), there is often in-effective initial transurethral resection of bladder tumour (TURBT) necessitating completion surgery [5] and poor compliance to guidelines [6]. Unified approaches are required to address this knowledge-practice divide, for example, the European Association of Urology (EAU) Guidelines Office introduced the IMAGINE project to improve guideline compliance [7]; conversely, quality indicators (QIs) both evaluate healthcare quality and (putatively) drive standards for better outcomes [8].

In 2008, The Scottish Government, recognising the need to improve cancer survival and address healthcare inequalities/variance published "Better cancer care, an action plan", mapping out key priorities and action plans to tackle cancer in Scotland; this included creation of QIs. Scotland's Quality Performance Indicator (QPI) programme aimed to foster a culture of continuous quality improvement by regular review of real-time data and consequently implement changes to improve patient-centred care, while reducing variance.

Following development (in collaboration with Scotland's Regional Cancer Networks, Information Services Division [ISD], and Healthcare Improvement Scotland), QPIs for BC were implemented within a framework of robust governance in 2014 [9]. Whilst ISD collected data on compliance, endpoints such as recurrence and progression (which better reflect outcomes in NMIBC) were not part of ISD's national dataset. Therefore, as part of a large clinical research project, we formed a clinician collaborative to carry out a series of studies on clinical outcomes and prognosis in BC; this current study is the first of the series and aimed at evaluating the quality of the initial TURBT, while describing its association with QPI compliance, tumour features, hospital volume, and surgeon category, consequent to the first 3 yr of BC QPI implementation.

2. Patients and methods

2.1. QPI data

Development of QPIs for BC began in 2012, with a multidisciplinary panel of specialists and patient representatives evaluating literature and guidelines to produce (initially) 11 QPIs, with data definitions, targets, and measurability criteria. These were enforced in April 2014. Supplementary Table 1 lists all 12 current pragmatic QPIs (the 12th generic QPI was added later).

The specific QPIs related to the quality of initial TURBT, which are of interest to this study, are as follows:

1 QPI 2(i)—use of a bladder diagram (Supplementary material) at the initial TURBT.
2 QPI 2(ii)—presence of detrusor muscle (DM) in the initial TURBT specimen.
3 QPI 3—use of a single post-TURBT instillation of mitomycin C (SPI-MMC) within 24 h following the initial TURBT.

An early re-TURBT in patients with high-risk NMIBC (HR-NMIBC) within 6 wk from the initial TURBT is mandated as QPI 4; however, in this current study, apart from its influence on policy and reporting presence/absence of residual cancer, we have not evaluated compliance/details around QPI 4 as it forms part of another study in the series.

National Health Service (NHS) Health Boards collected data prospectively on all new BC patients to include patient and tumour demographics, QPI variables, and pathology reports (using the Royal College of Pathologists' checklist [10]). Health Boards are accountable for reporting against QPIs and implementing service changes. Mandatory regional review of data was carried out annually for accuracy and compliance, and then published online by each network as snapshots, for example, 2014/2015, 2015/2016, and 2016/2017. A crucial agreement was that hospitals and surgeons were anonymised in published data.

2.2. Follow-up data

Clinical outcomes were prospectively recorded electronically in each hospital. Colleagues, representing the three networks, joined our clinical collaborative—QPI and follow-up data were pooled for a combined analysis of this "study

cohort". Only patients diagnosed with new BC between April 2014 and March 2017 were included. Strict agreement among collaborating clinicians, in the interest of inclusiveness and to encourage wide participation across Scotland in future, emphasised anonymity of individual hospitals/surgeons.

2.3. Definitions and assumptions

Please see the Supplementary material.

2.4. Endpoints

Endpoints representing quality of the initial TURBT in NMIBC [2,11] were as follows:

1 Recurrence rate at first follow-up cystoscopy (RRFFC).
2 Residual cancer rate at early re-TURBT in HR-NMIBC (residual cancer at re-TURBT).
3 Rate of finding T2 cancer at early re-TURBT in HR-NMIBC (T2 at re-TURBT).

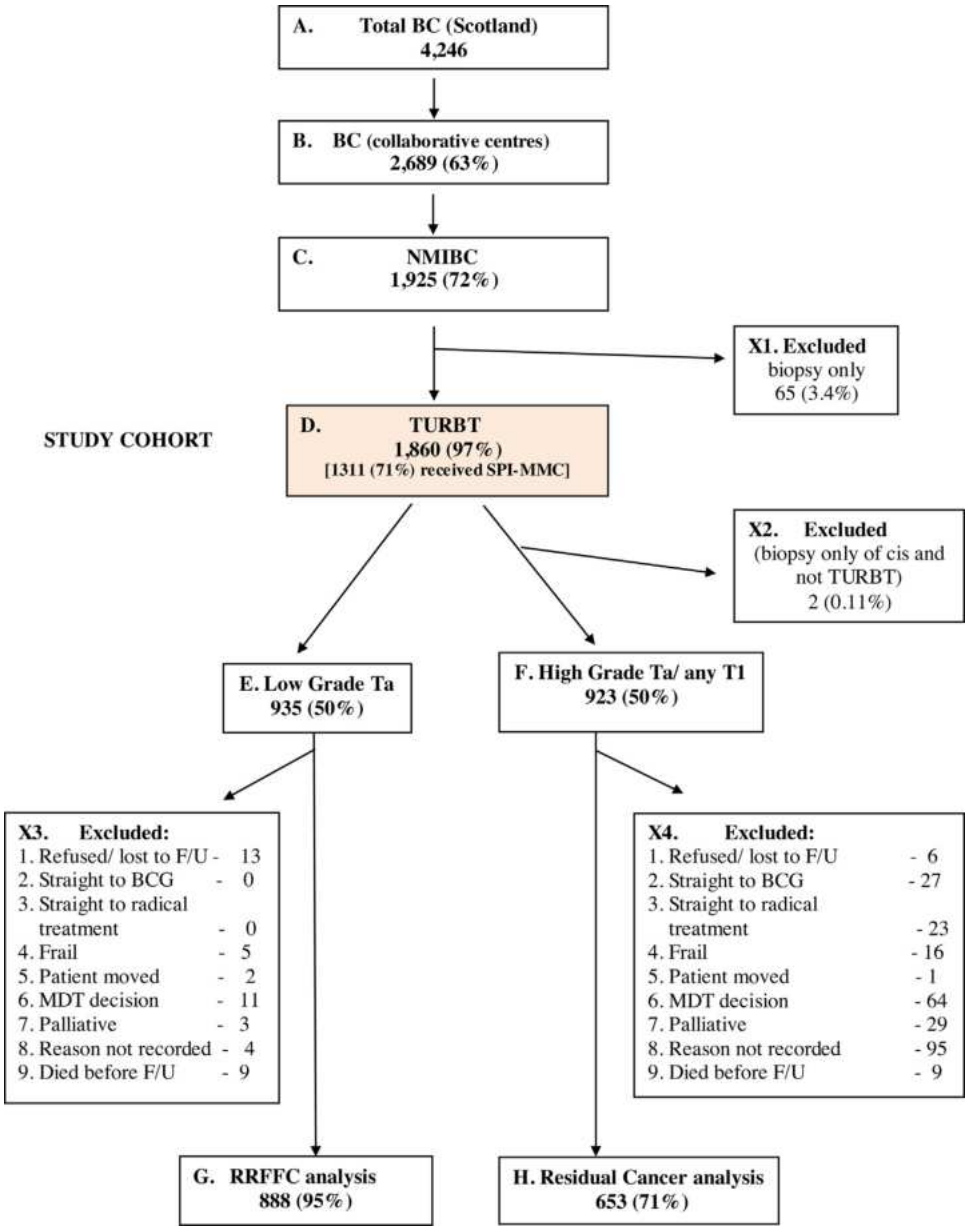


Fig. 1 – Flow chart of patient and cohort selection.
BC = bladder cancer; BCG = bacillus Calmette-Guerin; CIS = carcinoma in situ; F/U = follow-up; MDT = multidisciplinary team (this is when there has been a multidisciplinary team decision, including in some situations a comprehensive geriatric assessment, with recommendation that further regular surveillance is not in the patient's best interest, taking into account patient's general health and wishes); NMIBC = non–muscle-invasive bladder cancer; RRFFC = recurrence rate at first follow-up cystoscopy; SPI-MMC = single post-TURBT instillation of mitomycin C; TURBT = transurethral resection of bladder tumour.

Analysis was based on an "intention to treat" within the QPI framework and related agreements.

The exclusion criteria for analysis of endpoints are as follows:

1 Muscle-invasive bladder cancer at first TURBT.
2 Patients scheduled for palliative care only.
3 Biopsy and diathermy (fulguration) only (including for carcinoma in situ).
4 No follow-up yet/applicable.
5 Multidisciplinary team and/or comprehensive geriatric assessment recommendation that regular surveillance was not in the patient's best interest.

2.5. Statistical methodology

To illustrate compliance trends over the 3 yr, QPIs were clustered and stratified into snapshot audit years and hospital groups.

To determine which factors are associated with RRFFC, residual cancer, and T2 cancer at re-TURBT, we used a univariate logistic regression considering the following variables: (1) tumour size, number, grade, and stage (from the European Organisation for Research and Treatment of Cancer [EORTC] risk calculator); (2) bladder diagram, DM, and SPI-MMC (from QPI variables); and (3) hospital groups and surgeon category (additional a priori variables).

Variables statistically significant at 5% level were included in a multivariable logistic regression, and using forward selection, a final model was determined.

Association (post hoc) of categorical data across groups has been assessed using the Mantel-Haenszel test (for odds ratio) and chi-square test (for trends).

Additionally, post hoc logistic regression analyses were carried out to determine clinically relevant association between DM and SPI-MMC (as dependant variables) and tumour features, hospital group, and surgeon category to determine whether: (1) there was higher odds of obtaining DM in higher-volume hospitals, by consultants, in larger and/or multiple tumours, and (2) there was higher odds of using SPI-MMC in higher-volume hospitals, by consultants, and when it was more likely to be effective (ie, small, low-grade, and noninvasive tumours).

Analysis was completed using SPSS version 25 software.

3. Results

A total of 4246 consecutive patients had a new BC diagnosis in Scotland (between April 2014 and March 2017) [12].

Of these patients, 2689 (63%) were diagnosed in the centres taking part in this collaborative follow-up study—1925 (72%) had NMIBC (Fig. 1, Box C).

After excluding 65 (3.4%) patients who had only biopsy and fulguration of NMIBC (Fig. 1, Box X1), we had 1860 new NMIBC patients who had undergone TURBT (Fig. 1, Box D), that is, the "study cohort"; Table 1 describes patient/tumour demographics.

Table 1 – Demographics of patients with NMIBC in the "study cohort" (*N* = 1860) with tumour features, QPI compliance, surgeon categories, and hospital groups.

Variable		*n* (%)
Total patients included into TURBT for NMIBC analysis (*N*)		1860
Patient mean age, yr (range)		72.4 (21.1–97.7)
Gender	Male	1324 (71)
	Female	536 (29)
Tumour size	Small (<3 cm)	1199 (65)
	Large (≥3 cm)	619 (33)
	Not clearly specified	42 (2.2)
Tumour multiplicity	Single	1232 (66)
	Multiple	597 (32)
	Not clearly specified	31 (1.7)
Primary grade (WHO 2004)	Low grade	982 (53)
	High grade	876 (47)
	CIS	2 (0.1)
Primary stage	Ta	1304 (70)
	T1	554 (30)
	Tis	2 (0.1)
Use of a bladder diagram	Yes	1476 (79)
	No	383 (21)
	Not clearly specified	1 (0.11)
Use of SPI-MMC	Yes	1311 (71)
	No	481 (26)
	Not clearly specified	68 (3.7)
Detrusor muscle in initial TURBT specimen	Present	1424 (77)
	Absent	436 (23)
Surgeon category	Consultant	1197 (64)
	Specialist trainee	638 (34)
	Not clearly specified	25 (1.3)
Hospital group (by average number of TURBTs for NMIBC per year)	A (<60)	230 (12)
	B (60–90)	663 (36)
	C (>90)	967 (52)

CIS = carcinoma in situ; NMIBC = non–muscle-invasive bladder cancer; QPI = Quality Performance Indicator; SPI-MMC = single post-TURBT instillation of mitomycin C; TURBT = transurethral resection of bladder tumour; WHO = World Health Organization.

Table 2 reveals that most TURBTs were carried out by consultants, with the proportion of TURBTs performed by specialist trainees (STs) being the highest in high-volume centres (odds ratio [OR] = 2.25, 95% confidence interval [CI] = 1.84–2.75, $p < 0.001$). The odds of a consultant and ST operating on a patient with a large (≥3 cm) tumour were similar—35% (404/1158) and 32% (204/635), respectively (OR = 1.13, 95% CI = 0.92–1.39, $p = 0.2$). The odds of a consultant and ST operating on multiple tumours were also similar—34% (385/1140) and 31% (197/627), respectively (OR = 1.11, 95% CI = 0.90–1.37, $p = 0.3$; Table 2).

3.1. QPI compliance

Fig. 2A represents annual compliance with the selected QPIs in the whole of Scotland (obtained from the ISD publication [12]). The use of a bladder diagram increased significantly over the 3 yr. Close to 80% of TURBTs had DM in the specimen (this field was not reported separately in 2014/2015), while approximately two-thirds of the patients received SPI-MMC. Compliance trends in the "study cohort" appear to mirror the whole of Scotland (Fig. 2B).

Table 2 – Association between hospital groups, surgeon categories, tumour size, and multiplicity in the "study cohort" of patients undergoing TURBT for NMIBC (excluding those with unspecified data).

Hospital group, *n* (%)	Surgeon category, *n* (%)	Tumour size, *n* (%)	Tumour multiplicity, *n* (%)
A (<60 NMIBC TURBTs per year) 230 (12)	Consultant 149 (65)	<3 cm 109 (73)	Single 86 (79)
			Multiple 23 (21)
		≥3 cm 39 (26)	Single 25 (64)
			Multiple 11 (28)
	Specialist trainee 81 (35)	<3 cm 53 (65)	Single 38 (72)
			Multiple 15 (28)
		≥3 cm 28 (35)	Single 21 (75)
			Multiple 7 (25)
B (60–90 NMIBC TURBTs per year) 663 (36)	Consultant 500 (75)	<3 cm 338 (68)	Single 237 (70)
			Multiple 96 (28)
		≥3 cm 128 (26)	Single 90 (70)
			Multiple 36 (28)
	Specialist trainee 139 (21)	<3 cm 92 (66)	Single 68 (74)
			Multiple 21 (23)
		≥3 cm 45 (32)	Single 31 (69)
			Multiple 13 (29)
C (>90 NMIBC TURBTs per year) 967 (52)	Consultant 548 (57)	<3 cm 307 (56)	Single 202 (66)
			Multiple 104 (34)
		≥3 cm 237 (43)	Single 115 (49)
			Multiple 115 (49)
	Specialist trainee 418 (43)	<3 cm 286 (68)	Single 190 (66)
			Multiple 95 (33)
		≥3 cm 131 (31)	Single 82 (63)
			Multiple 46 (35)

NMIBC = non–muscle-invasive bladder cancer; TURBT = transurethral resection of bladder tumour.

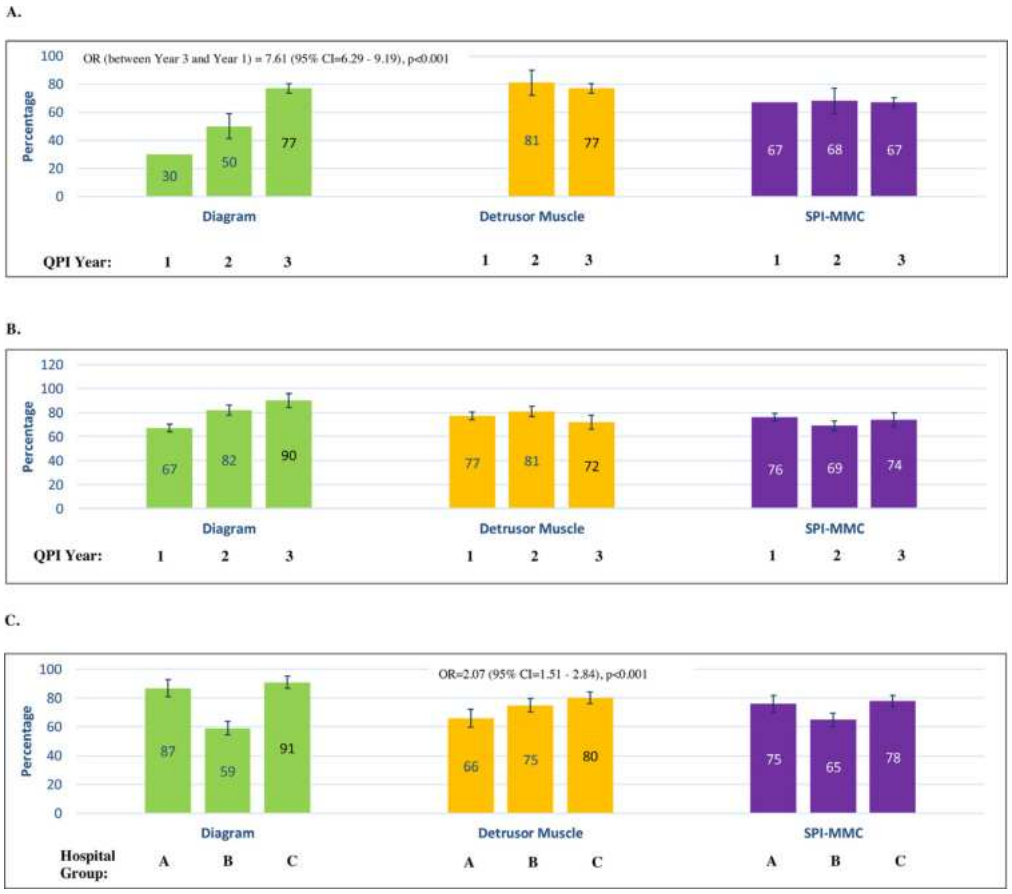


Fig. 2 – Compliance with NMIBC QPIs in the (A) whole of Scotland [12] stratified by QPI year, (B) "study cohort" stratified by QPI year, and (C) "study cohort" stratified by hospital group (hospitals are grouped by the average number of annual TURBTs for NMIBC—A, <60; B, 60–90; and C > 90 TURBTs). QPI year 1 = Apr 2014-Mar 2015; QPI year 2 = Apr 2015-Mar 2016; and QPI year 3 = Apr 2016-Mar 2017.
CI = confidence interval; NMIBC = non–muscle-invasive bladder cancer; OR = odds ratio; QPI = Quality Performance Indicator; SPI-MMC = single post-TURBT instillation of mitomycin C; TURBT = transurethral resection of bladder tumour.

Table 3 – Uni- and multivariable logistic regression analyses demonstrating association between tumour characteristics, surgeon category, and hospital groups with detrusor muscle (DM) status (excluding those with unspecified data).

Variable (*n*)		DM present (%)	DM absent (%)	Univariable OR (95% CI), *p* value	Multivariable OR (95% CI), *p* value
Size	<3 cm (1199)	913 (76)	286 (24)	1.13 (0.89–1.43), $p = 0.3$	–
	≥3 cm (619)	485 (78)	134 (22)		
Tumour number	Single (1232)	915 (74)	317 (26)	**1.61 (1.26–2.05), $p < 0.001$**	**1.52 (1.19–1.95), $p = 0.001$**
	Multiple (597)	491 (**82**)	106 (18)		
Tumour grade	LG (982)	748 (76)	234 (24)	1.04 (0.84–1.29), $p = 0.7$	–
	HG (876)	674 (77)	202 (23)		
Tumour stage	Ta (1304)	996 (76)	308 (24)	1.02 (0.81–1.30), $p = 0.8$	–
	T1 (554)	426 (77)	128 (23)		
Surgeon category	Consultant (1197)	932 (78)	265 (22)	1.21 (0.97–1.51), $p = 0.1$	–
	Specialist trainee (638)	475 (75)	163 (26)		
Hospital group	A (230)	152 (66)	78 (34)	**2.07 (1.51–2.84), $p < 0.001$**	**1.97 (1.44–2.72), $p < 0.001$**
	B (663)	497 (75)	166 (25)		
	C (967)	775 (**80**)	192 (20)		

CI = confidence interval; HG = high grade; LG = low grade; OR = odds ratio.
Values in bold font highlight statistically significant values.

When stratified by hospital groups (Fig. 2C), the proportion of TURBTs with DM present appeared to be larger in the higher-volume than in the low-volume centres. This association was independent of other variables on multivariable logistic regression analysis, while DM had increased odds of being present in TURBT of multiple tumours (Table 3). SPI-MMC had increased odds of being used in small, low-grade, and noninvasive tumours, and there was no statistical difference between consultants and trainees with regard to SPI-MMC utilisation (Table 4).

3.2. *Follow-up*

Almost 95% (888) of low-grade Ta (LGTa) patients had a first check cystoscopy (Fig. 1, Box G). Of the HR-NMIBC patients, following appropriate exclusions (Fig. 1, Box X4), 653 (70.8%) were suitable for analysis of residual cancer at re-TURBT (Fig. 1, Box H).

The overall rates of recurrence at 3 mo in LGTa and residual cancer in HR-NMIBC patients were 13% (116/888) and 33% (212/653), respectively. Trends in snapshot audit years 2014/2015, 2015/2016, and 2016/2017 revealed RRFFC values of 24% (39/287), 14% (43/305), and 12% (34/296; trend $x^2 = 0.58$, $p = 0.4$), while residual cancer in HR-NMIBC was seen in 35% (85/244), 31% (67/216), and 31% (60/193; trend $x^2 = 0.75$, $p = 0.4$), respectively. The overall risk of understaging HR-NMIBC at the initial TURBT was 2.9% (19/653).

Fig. 3 illustrates the association between hospital volume and surgeon category with RRFFC (Fig. 3A), and residual cancer at re-TURBT (Fig. 3B). Whilst there was no significant difference in overall RRFFC between high- and low-volume centres (OR = 1.6, 95% CI = 0.9–2.7, $p = 0.08$), the RRFFC following TURBT by consultants in the low-volume group appeared to be two-fold higher than that for a consultant in the high-volume group (OR = 2.1, 95% CI = 1.1–4.1, $p = 0.03$). This pattern was not seen in residual cancer at re-TURBT (Fig. 3B).

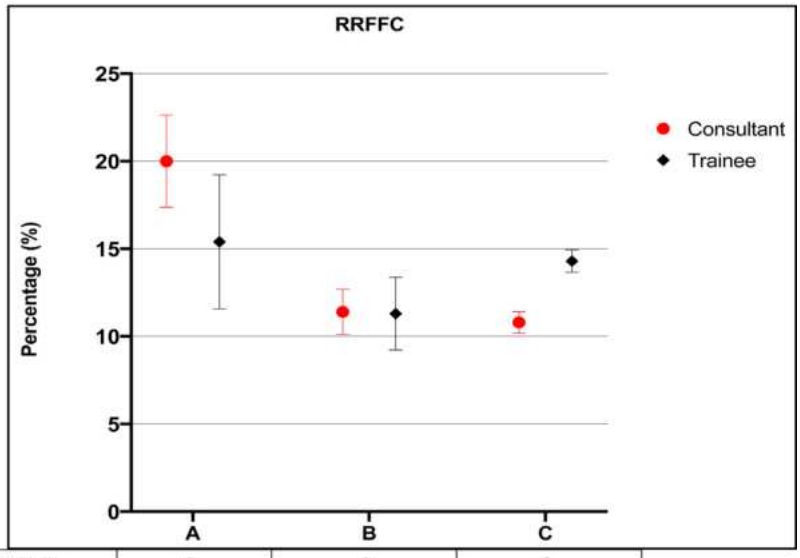
However, multivariable logistic regression analysis in LGTa tumours revealed SPI-MMC utilisation, and small tumours were independently associated with a three-fold lower RRFFC (Table 5). The apparent higher RRFFC in low-volume centres and multiple tumours did not reach statistical significance on multivariable analysis.

Table 4 – Uni- and multivariable logistic regression analysis demonstrating association between tumour characteristics, surgeon category, and hospital groups with SPI-MMC (excluding those with unspecified data).

Variable (*n*)		SPI-MMC Yes (%)	SPI-MMC No (%)	Univariable OR (95% CI), *p* value	Multivariable OR (95% CI), *p* value
Size	<3 cm (1199)	921 (**76.8**)	243 (20.3)	**2.22 (1.79–2.77), $p < 0.001$**	**2.05 (1.62–2.59), $p = 0.001$**
	≥3 cm (619)	370 (59.8)	217 (35.1)		
Tumour number	Single (1232)	881 (71.5)	307 (24.9)	1.05 (0.84–1.31), $p = 0.7$	–
	Multiple (597)	422 (70.7)	154 (36.5)		
Tumour grade	LG (982)	765 (**77.9**)	192 (19.6)	**2.09 (1.69–2.59), $p = 0.001$**	1.27 (0.97–1.67), $p = 0.08$
	HG (876)	546 (62.3)	287 (32.8)		
Tumour stage	Ta (1304)	1005 (**77.1**)	267 (20.5)	**2.61 (2.09–3.25), $p < 0.001$**	**1.87 (1.42–2.49), $p = 0.001$**
	T1 (554)	306 (55.5)	212 (38.3)		
Surgeon category	Consultant (1197)	824 (68.8)	327 (27.3)	**1.30 (1.04–1.64), $p = 0.02$**	1.03 (0.81–1.32), $p = 0.8$
	Specialist trainee (638)	477 (**74.8**)	145 (22.7)		
Hospital group	A (230)	170 (73.9)	55 (23.9)	**1.67 (1.36–2.08), $p = 0.001$**	1.59 (0.62–4.12), $p = 0.3$
	B (663)	416 (62.8)	222 (33.5)		
	C (967)	725 (**74.9**)	204 (21.1)		

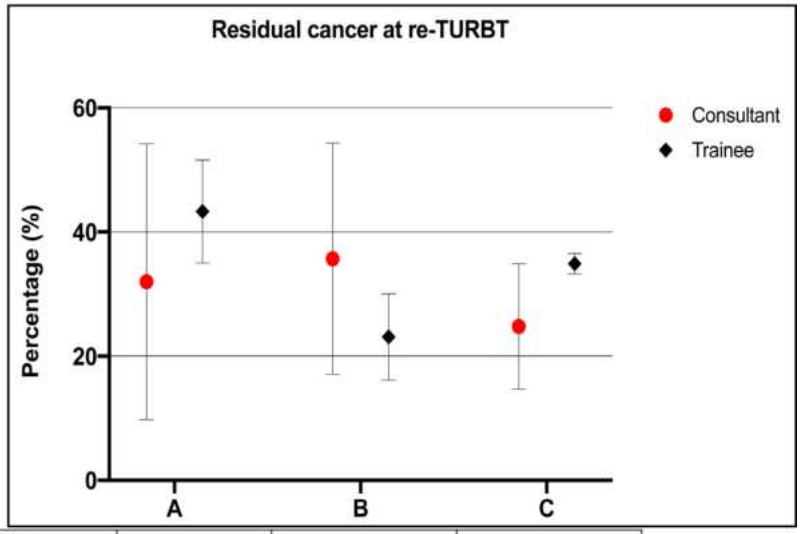
CI = confidence interval; HG = high grade; LG = low grade; OR = odds ratio; SPI-MMC = single post-TURBT instillation of mitomycin C; TURBT = transurethral resection of bladder tumour.
Values in bold font highlight statistically significant values.

A.



	Hospital group	A	B	C
N	Consultant TURBT	80	211	251
	Trainee TURBT	39	80	224
	Surgeon unclassified	0	3	0

B.



	Hospital group	A	B	C
N	Consultant TURBT	50	182	210
	Trainee TURBT	30	26	146
	Surgeon unclassified	0	8	1

Fig. 3 – (A) Recurrence rate at first follow-up cystoscopy (RRFFC) in hospital groups stratified by surgeon category (percentages with 95% confidence intervals). (B) Residual cancer at early re-TURBT in hospital groups stratified by surgeon category (percentages with 95% confidence intervals). TURBT = transurethral resection of bladder tumour.

In patients with HR-NMIBC, residual cancer at re-TURBT was independently associated with large and pT1 tumours (Table 5). Patients with residual cancer were apparently at lower odds of receiving SPI-MMC (Table 5). Absence of DM at initial TURBT in pT1 cancers carried a two-fold (OR = 2.0, 95% CI = 1.2–3.3, $p < 0.005$) added risk of residual cancer (41/78 = 53%) compared with those with DM present (121/343 = 35%).

Table 5 – Uni- and multivariable logistic regression analysis demonstrating the association between RRFFC ($n = 888$) and residual cancer and T2 at re-TURBT in HR-NMIBC ($n = 653$) with selected variables (excluding unspecified data for each variable).

Variable		Hospital group			Surgeon		Tumour multiplicity		Tumour size (cm)		Grade(WHO 2004)		Stage(TNM)		Bladder diagram		Detrusor muscle		SPI-MMC	
		A (%)	B (%)	C (%)	Consultant (%)	Specialist trainee (%)	1 (%)	>1 (%)	<3 (%)	≥3 (%)	LG (%)	HG (%)	pTa (%)	pT1 (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
LGTa (n)		119	294	475	542	343	646	232	688	187	888	NA	888	NA	719	168	677	211	716	153
RRFFC	Yes	22 (19)	35 (12)	59 (12)	67 (12)	47 (14)	75 (12)	38 (16)	64 (9.3)	48 (**26**)	116 (13)	NA	116 (13)	NA	88 (12)	27 (16)	88 (13)	28 (13)	72 (10)	40 (**26**)
	No	97	259	416	475	296	571	194	624	139	772	NA	772	NA	631	141	589	183	644	113
Univariate OR (95% CI), *p* value		1.59 (0.94–2.74), *p* = 0.09			1.12 (0.75–1.68), *p* = 0.6		1.49 (0.98–2.28), *p* = 0.06		**3.37 (2.22–5.11), *p* < 0.001**		NA		NA		1.37 (0.86–2.19), *p* = 0.1		1.02 (0.65–1.62), *p* = 0.5		**3.17 (2.05–4.89), *p* < 0.001**	
Multivariate OR (95% CI), *p* value		–			–		–		**3.29 (2.14–5.03), *p* = 0.001**		–		–		–		–		**3.05 (1.95–4.79), *p* = 0.001**	
HR-NMIBC (n)		80	216	357	442	202	381	261	334	295	42	611	232	421	521	132	523	130	422	206
Residual cancer at re-TURBT	Yes	29 (36)	79 (37)	104 (29)	133 (30)	70 (35)	117 (31)	90 (35)	84 (25)	117 (**40**)	9 (21)	203 (33)	50 (22)	162 (**39**)	165 (32)	47 (36)	162 (31)	50 (39)	100 (24)	103 (**50**)
	No	51	137	253	309	132	264	171	250	178	33	408	182	259	356	85	361	80	322	103
Univariate OR (95% CI), *p* value		1.38 (0.83–2.30), *p* = 0.2			1.23 (0.87–1.76), *p* = 0.2		1.18 (0.85–1.66), *p* = 0.3		**1.96 (1.39–2.75), *p* < .001**		1.82 (0.86–3.88), *p* = 0.1		**2.28 (1.57–3.29), *p* < 0.001**		1.19 (0.80–1.78), *p* = 0.4		1.39 (0.94–2.08), *p* = 0.1		**3.22 (2.26–4.59), *p* < 0.001**	
Multivariate OR (95% CI), *p* value		–			–		–		**1.66 (1.16–2.36), *p* = 0.005**		–		**2.03(1.38–2.98), *p* = 0.001**		–		–		**2.90 (2.02–4.17), *p* = 0.001**	
T2 at re-TURBT	Yes	4 (5.0)	3 (1.4)	12 (3.4)	9 (2.0)	10 (**4.9**)	8 (2.1)	10 (3.8)	6 (1.8)	13 (4.4)	0 (0.0)	19 (3.1)	1 (0.4)	18 (**4.3**)	17 (3.3)	2 (1.5)	15 (2.9)	4 (3.1)	7 (1.6)	11 (**5.3**)
	No	76	213	345	433	192	373	251	328	282	42	592	231	403	504	130	508	126	415	195
Univariate OR (95% CI), *p* value		3.74 (0.82–17.1), *p* = 0.07			**2.51 (1.00–6.27), *p* = 0.04**		1.86 (0.72–4.77), *p* = 0.2		2.52 (0.95–6.72), *p* = 0.06		NA		**10.3 (1.37–77.8), *p* = 0.01**		2.19 (0.50–9.61), *p* = 0.3		1.08 (0.35–3.29), *p* = 0.9		**3.34 (1.28–8.76), *p* = 0.009**	
Multivariate OR (95% CI), *p* value		–			**2.76 (1.01–7.04), *p* = 0.03**		–		–		–		**9.26 (1.22–71.43), *p* = 0.03**		–		–		**2.99 (1.13–7.9), *p* = 0.03**	

CI = confidence interval; HG = high grade; HR-NMIBC = high-risk non–muscle-invasive bladder cancer; LG = low grade; NA = not applicable; OR = odds ratio; RRFFC = recurrence rate at first follow-up cystoscopy; SPI-MMC = single post-TURBT instillation of mitomycin C; TNM = tumour, node, metastasis; TURBT = transurethral resection of bladder tumour; WHO = World Health Organization.
Values in bold font highlight statistically significant values.

With a very small risk of initial TURBT understaging HR-NMIBC (9/653), the CIs for analyses of association were wide: TURBTs by trainees, and T1 tumours appeared to be associated with a higher risk of understaging (Table 5).

4. Discussion

Scotland's QPI programme for BC, to our knowledge, is the first national initiative to not only develop (September 2013) and implement (April 2014) QIs, but also evaluate compliance within a framework of governance and prospective audit (April 2014 onwards), and gauge clinical outcomes. Our unique position with maturity of this process has allowed many lessons to be learnt [12]. From this large real-world cohort representing approximately two-thirds of patients treated in Scotland, we are proud to note the high compliance with QPIs and quality of TURBT.

Lawrence and Olesen [13] defined QI as "a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality, of care provided", and Donabedian [8] proposed principles that underpin their development. However, developing achievable QIs is understandably complex [14] as is its implementation, having to take into account multiple facets (including behavioural) in addressing knowledge-practice gaps [15] with multilayered interventions required to improve compliance [16]. The Donabedian [8] principles—*structure, process*, and *outcome*—appear to be embedded in our 12 QPIs [12]. Despite the absence of clinical outcomes from any other BC QI programme (to our knowledge), recommendations for QIs abound [17–21].

We consider the effectiveness of initial TURBT vital to the patient journey and determinants of its quality, as surrogates of "attention to detail"; QPI 2, in particular, was developed from Scottish projects [22,23], building on the work by Brausi and colleagues [2,24]. The diagram with documentation of tumour features is recommended by the EAU [25] and checklists [18,26]. Whilst documentation of tumour location(s) has several technical benefits (eg, guiding re-TURBT, especially when the initial TURBT was performed by a different surgeon), it has accepted prognostic implications, particularly in HR-NMIBC [27]. Conversely, the absence of DM has been associated with a higher risk of residual cancer and understaging in HR-NMIBC [22,28]—our cohort suggests this association, while emphasising selective re-TURBT in pT1 cancers.

The Scottish National Dataset [12] reveals exceptionally high compliance to SPI-MMC when compared with other European and North American data [6]. Whilst MMC has been the UK standard, other agents could be alternatives [25]. Our use of MMC consistently across Scotland means that the observed outcomes are more likely a consequence of SPI-MMC rather than potentially differing efficacy of intravesical chemotherapy agents. SPI-MMC is not recommended as the sole intravesical adjunct in HR-NMIBC; however, with the inability to reliably predict grade in new BC [29] and its relative safety, wider (responsible) usage is more likely to benefit the most appropriate patients. Our QPI target of 60% (Supplementary Table 1) was designed to allow for clinician discretion in using SPI-MMC and contraindications [12] (the effectiveness of this selective utilisation is evident from Table 4), and along with other confounders (eg, suspicion of perforation), are reasonable explanations to the observed (albeit, intriguing) inverse relationship between SPI-MMC and residual cancer.

The International Bladder Cancer Group recommends using recurrence rates as endpoints for LGTa [30]. We selected our endpoints (1) because recurrence at 3 mo and residual cancer in HR-NMIBC are strong predictors of future recurrence [31] and progression [28], respectively, and (2) to ensure consistency with previously described TURBT quality measures [2,11]. Reassuringly, RRFFC for LGTa in our real-world cohort is low, when compared with clinical trials [31,32].

Tumour multiplicity at presentation, in our study, does not appear to be as strong a predictor of early recurrence as seen in the EORTC trials [31]. Perhaps, the variability of resection quality in this historical series [2] was responsible. Nevertheless, this paradigm shift towards improved recurrence and staging accuracy with TURBT will benefit from contemporaneous prognostic prediction to facilitate stratification of NMIBC patients—upcoming long-term results might be timely.

ISD's publications [12] have maintained hospital anonymity, and a fundamental agreement in our collaborative was to preserve this anonymity. However, having observed an unlikely association between SPI-MMC and HR-NMIBC, post hoc hospital group analyses were necessary to obtain granularity. This led to our, possibly novel yet intriguing, observations around hospital volume–TURBT relationship. Nonetheless, recurrence is also influenced by surveillance precision: it is possible, for example, that larger hospitals might rely on less experienced staff (perhaps trainees) who might miss small subtle recurrences, while an experienced small centre consultant could be more accurate, causing apparently "higher" early recurrence rates.

Surgeon experience can determine TURBT quality [2,22,23]. Not unexpectedly, consultant:trainee TURBT ratios appeared to shift in favour of trainees in higher-volume centres. Contrary to belief, trainees did not appear to be excluded from operating on large and/or multiple tumours and were as likely as consultants to use SPI-MMC. Reassuringly, outcomes between consultants and trainees were not (statistically) dissimilar, and this is testament to our policy on supervision created at QPI inception.

It is our a priori position that implementation of the QPI programme, with associated audit and governance processes, has resulted in positive outcomes for Scotland's NMIBC patients. Implementation science suggests that processes that incorporate "audit and feedback" (as in the QPI programme) have potential to improve outcomes within healthcare systems [16] and perhaps the natural "scrutiny" within a large public healthcare system, such as the NHS, favours better outcomes when performance targets are applied [33].

4.1. Limitations

We lacked a planned (pre-QPI) cohort for comparison; however, the rates of absent DM and recurrence/residual cancer appear to be lower than in two pre-QPI Scottish cohorts [22,23]. Additionally, as we were prospectively audited, the Hawthorne effect would likely improve outcomes over any historical cohort. Our agreement, at the outset, to maintain hospital and surgeon anonymity precluded carrying out hierarchical modelling, which would have given additional granularity to the analyses. Re-TURBT included selective cystoscopy/biopsy—we accept this as representing pragmatic real-world practice, as is the small possibility that some patients received adjuvant intravesical chemotherapy before their first check cystoscopy. A central pathologist was not involved; however, regional uropathologists reporting all biopsies, use of the Royal College of Pathologists' checklist [10] (QPI 5), and multidisciplinary review (QPI 1) ensured uniform standards. As all TURBTs performed by trainees were intended to be supervised, the surgeon category, when ascribed to a trainee, might still reflect consultant contribution. Voluntary participation in the collaborative could cause a small selection bias, despite representing two-thirds of Scotland's TURBTs.

5. Conclusions

By focusing on a package of evidence-based QIs, Scotland's QPI programme appears to facilitate high-quality TURBT. In a real-world setting, it is associated with low early recurrence/residual cancer with accurate pathological staging, while compliance with use of a single post-TURBT instillation of chemotherapy reduced the risk of early recurrence in LGTa cancer significantly. These results have allowed for modifications to relevant QPIs since 2017, while setting pragmatic benchmarks for TURBT.

***Author contributions*:** Paramananthan Mariappan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Mariappan.
Acquisition of data: Mariappan, Johnston, Padovani, Clark, Thomas, Simpson, Hollins, Hasan, Trail, Hamid, Bhatt, Hendry, Ahmad.
Analysis and interpretation of data: Mariappan.
Drafting of the manuscript: Mariappan.
Critical revision of the manuscript for important intellectual content: Mariappan, Hendry, Bhatt, Hollins, Ahmad, Thomas.
Statistical analysis: Mariappan.
Obtaining funding: None.
Administrative, technical, or material support: Mariappan, Ahmad, Bhatt, Nandwani, Mitchell, Hollins, Hendry, Thomas.
Supervision: Mariappan, Ahmad, Bhatt, Nandwani, Mitchell, Hollins, Hendry, Thomas.
Other: None.

Financial disclosures: Paramananthan Mariappan certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

***Acknowledgements*:** We are very grateful to all colleagues involved in the patient journey and collection of data. Special thanks to: Dr. Lorna Bruce, SCAN audit manager; all audit personnel from the three networks: SCAN, WoSCAN, and NoSCAN; Dr. Hillary Dobson (chair) and Jennifer Doherty of the National Cancer Quality Steering Group; and the Information Services Division (ISD) of NHS Scotland. We would like to thank Dr. Catriona Graham, PhD, lead statistician of the Wellcome Trust Clinical Research Facility, Edinburgh, Scotland for her input and guidance in the statistical methodology. The authors are very grateful to Professor James Catto, editor in chief of *European Urology*, and the expert reviewers for their recommendations and guidance during the review process, which have enhanced the quality of our article.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.051.

References

[1] De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol 2014;15:23–34.
[2] Brausi M, Collette L, Kurth K, et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523–31.
[3] Advanced Bladder Cancer Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:189–99, discussion 199–201.
[4] James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477–88.
[5] Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol 2003;170(2 Pt 1):433–7.
[6] van Rhijn BW, Burger M. Bladder cancer: low adherence to guidelines in non-muscle-invasive disease. Nat Rev Urol 2016;13:570–1.
[7] Briganti A, MacLennan S, Marconi L, Plass K, N'Dow J, Project EAUGOI. European Association of Urology (EAU) guidelines: do we care? Reflections from the EAU Impact Assessment of Guidelines Implementation and Education Group. BJU Int 2016;117:850–1.
[8] Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q 1966;44(3 Suppl):166–206.
[9] Healthcare Improvement Scotland. Bladder cancer clinical quality performance indicators. http://www.healthcareimprovementscotland.org/his/idoc.ashx?docid=1d5bd547-316d-49b0-8948-e2aed407a660&version=-1 2014
[10] Shanks J, Chandra A, McWilliam L, Varma M. Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra). ed. 2. Royal College of Pathologists https://www.rcpath.org/uploads/assets/e2c11ff6-780a-471e-a21a4dc48788d35b/Dataset-for-tumours-of-the-urinary-collecting-system-renal-pelvis-ureter-urinary-bladder-and-urethra.pdf 2013

[11] Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int 2008;102(9 Pt B):1242–6.
[12] Information Services Division, NHS National Services Scotland. Bladder cancer quality performance indicators: patients diagnosed between April 2014 and March 2017. 2018. https://www.isdscotland.org/Health-Topics/Quality-Indicators/Publications/2018-08-28/2018-08-28-Bladder-QPI-Report.pdf?774782897.
[13] Lawrence M, Olesen F. Indicators of quality in health care. Eur J Gen Pract 1997;3:103–8.
[14] Campbell SM, Braspenning J, Hutchinson A, Marshall M. Research methods used in developing and applying quality indicators in primary care. Qual Saf Health Care 2002;11:358–64.
[15] Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care 2005;14:26–33.
[16] French SD, Green SE, O'Connor DA, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. Implement Sci 2012;7:38.
[17] Goossens-Laan CA, Kil PJ, Roukema JA, Bosch JL, De Vries J. Quality of care indicators for muscle-invasive bladder cancer. Urol Int 2011;86:11–8.
[18] Montgomery JS, Miller DC, Weizer AZ. Quality indicators in the management of bladder cancer. J Natl Compr Canc Netw 2013;11:492–500.
[19] Khare SR, Aprikian A, Black P, et al. Quality indicators in the management of bladder cancer: a modified Delphi study. Urol Oncol 2017;35:328–34.
[20] Akand M, Muilwijk T, Raskin Y, De Vrieze M, Joniau S, Van Der Aa F. Quality control indicators for transurethral resection of non-muscle-invasive bladder cancer. Clin Genitourin Cancer 2019;17:e784–92.
[21] Cooperberg MR, Porter MP, Konety BR. Candidate quality of care indicators for localized bladder cancer. Urol Oncol 2009;27:435–42.
[22] Mariappan P, Zachou A, Grigor K. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol 2010;57:843–9.
[23] Mariappan P, Finney SM, Head E, et al. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU Int 2012;109:1666–73.
[24] Brausi M, Sylvester R, van der Meijden A, Kurth K. Does the surgeon have an impact in the outcome of patients with Ta-T1 TCC of the bladder? Results of an EORTC quality control study on TURBT. Eur Urol 2001;39(Suppl 5):119.
[25] Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013;64:639–53.
[26] Pan D, Soloway MS. The importance of transurethral resection in managing patients with urothelial cancer in the bladder: proposal for a transurethral resection of bladder tumor checklist. Eur Urol 2012;61:1199–203.
[27] Palou J, Sylvester RJ, Faba OR, et al. Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. Eur Urol 2012;62:118–25.
[28] Gontero P, Sylvester R, Pisano F, et al. The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/grade 3 bladder cancer treated with bacille Calmette-Guerin. BJU Int 2016;118:44–52.
[29] Mariappan P, Lavin V, Phua CQ, Khan SAA, Donat R, Smith G. Predicting grade and stage at cystoscopy in newly presenting bladder cancers—a prospective double-blind clinical study. Urology 2017;109:134–9.
[30] Matulay JT, Soloway M, Witjes JA, et al. Risk-adapted management of low-grade bladder tumours: recommendations from the International Bladder Cancer Group (IBCG). BJU Int 2020;125:497–505.
[31] Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–77.
[32] O'Brien T, Ray E, Chatterton K, Khan MS, Chandra A, Thomas K. Prospective randomized trial of hexylaminolevulinate photodynamic-assisted transurethral resection of bladder tumour (TURBT) plus single-shot intravesical mitomycin C vs conventional white-light TURBT plus mitomycin C in newly presenting non-muscle-invasive bladder cancer. BJU Int 2013;112:1096–104.
[33] The Health Foundation. Evidence scan: the impact of performance targets within the NHS and internationally. In: http://www.health.org.uk/sites/default/files/TheImpactOfPerformanceTargetsWithinTheNHSAndInternationally_0.pdf 2015

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 520–530 of this issue

National Quality Improvement Program in Transurethral Resection of Bladder Tumor: A Model for the Rest of Us, Even if We Cannot Share All Results

Ankeet Shah, Wei Phin Tan, Brant A. Inman *

Division of Urology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

It is increasingly clear that variability in practice patterns and quality improvement efforts affect survival outcomes in bladder cancer. In this issue of *European Urology*, Mariappan et al [1] present the first part of their comprehensive quality improvement program for bladder cancer, impressively implemented at a national level in Scotland. This first publication deals with quality in transurethral resection of bladder tumor (TURBT) procedures.

The authors evaluated 1860 new patients with non–muscle-invasive bladder cancer (NMIBC) for 3 yr after implementation of a quality improvement program in terms of compliance with quality metrics (eg, use of a bladder diagram for documenting lesions, inclusion of detrusor muscle in the TURBT specimen, and use of post-TURBT mitomycin C) and oncologic outcomes. The study is limited by the absence of a control group before implementation of the quality program, lack of central pathology review, and lack of demonstrable standardized access to enhanced technology for TURBT (eg, blue light endoscopy). In addition, Scotland is a relatively small country, which could make implementation easier than in larger and more heterogeneous places. However, this real-world study reflects a tremendous effort and national commitment to quality and represents the kinds of steps to standardize and improve care that all urologists should emulate. The tangible benefits of lower recurrence rates, less residual disease at repeat TURBT, and more accurate staging are important to patients.

Underlying this study is a fundamental question: what constitutes high-quality TURBT? Oncologic outcomes speak most definitively to the quality of TURBT (less recurrence/progression is better), but these events occur years after the procedure and are therefore not measurable at the time of an operation. Endpoints such as those proposed by the International Bladder Cancer Group can take too long to occur in order to be useful for quality improvement in real time [2,3]. Proxy outcomes such as those used in this study (recurrence at first cystoscopy and residual disease at repeat TURBT) allow providers and systems to optimize care with more agility. In an effort to shift assessment of quality to an even earlier point, it may be appropriate to define quality in part as compliance with guideline-based practice, especially given the body of knowledge we have regarding specific clinical factors that improve outcomes. For example, we have clear data on reduction of recurrence rates with immediate postoperative intravesical chemotherapy, enhanced accuracy of staging with detrusor muscle in the pathology specimen, and upstaging rates with repeat TURBT for high-risk NMIBC. In addition, multiple studies have demonstrated the benefits of appropriate documentation of lesion location with diagrams and checklists at the time of TURBT [4]. However, the factors of experience and technique that affect outcomes remain, and it is less clear how to evaluate these. It would have been nice if variations in outcomes between patients were modeled at the patient level (tumor size, stage, grade, multifocality), physician level (age, annual volume, TUR technique), and hospital level (annual volume, resource availability) to determine where variability in outcomes occurs. Clearly, the doctor cannot be blamed for everything.

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.051.
* Corresponding author. Division of Urology, Duke Cancer Institute, Duke University Medical Center, 3007 Snyderman Building, 905 La Salle Street, Durham, NC 27710, USA. Tel. +1 919 6815946; Fax: +1 919 6687093.
E-mail address: brant.inman@duke.edu (B.A. Inman).

https://doi.org/10.1016/j.eururo.2020.07.020

Once quality is defined and benchmarks are established, the critical step in improving quality of care is determining how to facilitate standardization across sites and improve. Regular reports shared with participants can help providers and institutions understand their performance relative to their peers and take corrective actions. However, those who have developed quality programs are acutely aware that findings cannot always be shared publicly owing to agreements about surgeon- and hospital-level confidentiality, which are fundamental to building the quality program in the first place [1,5]. Quality programs may reveal findings regarding specific providers or centers who performed poorly on certain metrics relative to their peers because they treat higher-risk patients.

Does the public have a right to know that a particular medical center has worse or better outcomes? Or should individual providers' and institutions' data be anonymous, as is the case with the American College of Surgeons National Surgical Quality Improvement Program (NSQIP)? The assumption here is that analysis of quality metrics should be accurate, which can never be said with 100% certainty. Moreover, institutional composition is fluid. When a high-volume provider moves, does he leave behind an institution that can continue to deliver the same quality of care?

Should compensation take into account individual providers' or institutions' quality metrics? This is a controversial topic, especially in non-nationalized health systems, due in part to the ethical considerations raised by the possibility that patients' access to quality care will be partly driven by socioeconomic factors. Supporters of value-based care note successful application of such approaches in primary care and non–fee-for-service health systems without definitively adverse effects on access to care [6,7]. At the end of the day, money clearly talks.

If quality metrics highlight significant variation in care, should resources be devoted to mitigating the effects of such variation at each site, or should care be centralized in centers of excellence? The answer probably depends on what the drivers of the outcome variation are. For example, the case mix at an inner city medical center serving a patient population with low socioeconomic status will always have different outcomes to a boutique "fly in" center for the rich. If the issue is access to better technology to facilitate optimal resection, then health system resource allocation needs adjustment. However, if the driver has more to do with expertise or surgeon comfort, centralization of care offers the opportunity to minimize variation of care and positively impact oncologic outcomes, provided that patients can still get care [8]. Some patients will not accept a 6-h journey for cystoscopy and TURBT. Much work is required to better understand what the consequences are for patient-reported outcomes and access to care [9].

Mariappan et al [1] have demonstrated the utility of a highly structured quality program in optimizing outcomes of TURBT and provide an example of how we urologists need to organize in order to improve. We look forward to seeing the rest of the bladder cancer quality improvement data from this program to learn how participating surgeons adjust their own behavior based on these preliminary findings.

Conflicts of interest: Brant A. Inman is a consultant/advisor for Fergene, Genentech, and Combat Medical, and an investigator for Genentech, QED Therapeutics, Dendreon, Combat Medical, FKD Therapies, Taris Biomedical, and Nucleix. Ankeet Shah and Wei Phin Tan have nothing to disclose.

References

[1] Mariappan P, Johnston A, Padovani L, et al. Enhanced quality and effectiveness of transurethral resection of bladder tumour in non–muscle-invasive bladder cancer: a multicentre real-world experience from Scotland's Quality Performance Indicators programme. Eur Urol 2020;78:520–30.

[2] Matulay JT, Soloway M, Witjes JA, et al. Risk-adapted management of low-grade bladder tumours: recommendations from the International Bladder Cancer Group (IBCG). BJU Int 2020;125:497–505.

[3] Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. J Clin Oncol 2016;34:1935–44.

[4] Leow JJ, Catto JWF, Efstathiou JA, et al. Quality indicators for bladder cancer services: a collaborative review. Eur Urol 2020;78:43–59.

[5] Montie JE, Linsell SM, Miller DC. Quality of care in urology and the Michigan Urological Surgery Improvement Collaborative. Urol Pract 2014;1:74–8.

[6] Darves-Bornoz AL, Resnick MJ. The evolution of financial incentives in the U.S. health care system. Urol Oncol 2017;35:1–4.

[7] Tao W, Agerholm J, Burström B. The impact of reimbursement systems on equity in access and quality of primary care: a systematic literature review. BMC Health Serv Res 2016;16:542.

[8] Casey MF, Wisnivesky J, Le VH, et al. The relationship between centralization of care and geographic barriers to cystectomy for bladder cancer. Bladder Cancer 2016;2:319–27.

[9] Williams SB, Ray-Zack MD, Hudgins HK, et al. Impact of centralizing care for genitourinary malignancies to high-volume providers: a systematic review. Eur Urol Oncol 2019;2:265–73.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority Brief Correspondence

Editorial by Douglas G. Ward, Roland Arnold and Richard T. Bryan on pp. 538–539 of this issue.

Identification of Differential Tumor Subtypes of T1 Bladder Cancer

A. Gordon Robertson [a], Clarice S. Groeneveld [b,c], Brian Jordan [d], Xiquo Lin [e], Kimberly A. McLaughlin [f], Arighno Das [f], Leigh Ann Fall [f], Damiano Fantini [f], Timothy J. Taxter [h], Lauren S. Mogil [i], Sia Viborg Lindskrog [j], Lars Dyrskjøt [j], David J. McConkey [k], Robert S. Svatek [l,m], Aurélien de Reyniès [b], Mauro A.A. Castro [n], Joshua J. Meeks [f,g,]*

[a] *Dxige Research Inc., Courtenay, BC, Canada;* [b] *Cartes d'Identité des Tumeurs Program, Ligue Nationale Contre le Cancer, Paris, France;* [c] *Oncologie Moleculaire, Institut Curie, Equipe Labellisée Ligue Contre le Cancer, Paris, France;* [d] *Department of Urology, University of Washington, Seattle, WA, USA;* [e] *Department of Pathology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA;* [f] *Departments of Urology, Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA;* [g] *Jesse Brown VA Medical Center, Chicago, IL, USA;* [h] *Tempus Labs, Inc., Chicago, IL, USA;* [i] *Center for Translational Data Science, University of Chicago, Chicago, IL, USA;* [j] *Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark;* [k] *Johns Hopkins Greenberg Bladder Cancer Institute, Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA;* [l] *Experimental Developmental Therapeutics Program, UT Health MD Anderson, San Antonio, TX, USA;* [m] *Department of Urology, UT Health San Antonio, San Antonio, TX, USA;* [n] *Bioinformatics and Systems Biology Laboratory, Federal University of Paraná, Curitiba, Brazil*

Article info

Article history:
Accepted June 22, 2020

Associate Editor:
James Catto

Statistical Editor:
Emily Zambor

Keywords:
Non–muscle-invasive bladder cancer
Bacillus Calmette-Guérin
Carcinoma in situ
Immune signatures
Tumor subtype
Luminal

Abstract

Stage T1 bladder cancers have the highest progression and recurrence rates of all non–muscle-invasive bladder cancers (NMIBCs). Most T1 cancers are treated with bacillus Calmette-Guérin (BCG), but many will progress or recur, and some T1 patients will die from bladder cancer. Particularly aggressive tumors could be treated with early cystectomy. To better understand the molecular heterogeneity of T1 cancers, we performed transcriptome profiling and unsupervised clustering, and identified five consensus subtypes of T1 tumors treated with repeat transurethral resection (reTUR) and induction and maintenance BCG. The T1-LumGU subtype was associated with carcinoma in situ (CIS; six/13, 46% of all CIS), had high E2F1 and EZH2 expression, and was enriched in E2F target and G2M checkpoint hallmarks. The T1-Inflam subtype was inflamed and infiltrated with immune cells. While most T1 tumors were classified as luminal papillary, the T1-TLum subtype had the highest median luminal papillary score and FGFR3 expression, no recurrence events, and the fewest copy number gains. T1-Myc and T1-Early subtypes had the most recurrences (14/30 within 24 mo), the highest median MYC expression, and, when combined, had significantly worse recurrence-free survival than the other three subtypes. T1-Early had five (38%) recurrences within the first 6 mo of BCG, and repressed IFN-α and IFN-γ hallmarks and inflammation. We developed a single-patient T1 classifier and validated our subtype biology in a second cohort of T1 tumors. Future research will be necessary to validate the proposed T1 subtypes and to determine if therapies can be individualized for each subtype.

Patient summary: We identified and characterized expression subtypes of high-grade stage T1 bladder cancer that are biologically heterogeneous and have variable responses to bacillus Calmette-Guérin treatment. We validated the subtypes and describe a single-patient classifier.

* Corresponding author. Department of Urology, Feinberg School of Medicine, Northwestern University, 676 N St Clair Suite 2300 Chicago, IL 60611, USA. Tel. +1 312-694-9001 Fax: +1 312-694-9000.
E-mail address: joshua.meeks@northwestern.edu (J.J. Meeks).

https://doi.org/10.1016/j.eururo.2020.06.048
0302-2838/Published by Elsevier B.V. on behalf of European Association of Urology.

T1 tumors are potentially the most aggressive subtype of non–muscle-invasive bladder cancer (NMIBC), with 40% recurrence and 15% progression at 5 yr [1]. While most T1 cancers are treated with bacillus Calmette-Guérin (BCG), recurrence or progression is treated with radical cystectomy, and delayed intervention is associated with lower survival [1]. Biomarkers that could predict response to BCG in T1 cancers could help both patients and clinicians in making treatment-related decisions; however, few to no tumor-specific prognostic features have been identified. We previously reported that T1 and MIBC cancers had similar mutations, but that mutations were unable to predict response to BCG [2]. The primary objective of our study was to investigate the molecular heterogeneity of T1 cancers via RNA sequencing of 73 primary T1 tumors (Supplementary Table 1A) with a primary endpoint of recurrence after BCG. To minimize sources of bias, all tumors were treated at the same institution, 84% had repeat transurethral resection, and all received induction and maintenance BCG (64%) if they did not recur. The recurrence rate was 32% (23/73) at 24 mo and 25% (18/73) at 1 yr, with progression in 8% (six/73) at 24 mo (Supplementary Table 1A, Supplementary Fig. 1). We focused our analysis on tumor expression subtypes identified via unsupervised consensus clustering. After assessing three-, four-, and five-cluster solutions (Supplementary Fig. 2), we characterized a five-cluster solution whose subtypes had distinct clinical outcomes and biological characteristics (Fig. 1). We combined gene expression, gene-set enrichment, and regulon analyses to describe the distinct biology for each subtype (Supplementary methods) [3].

The T1-luminal genomically unstable (T1-LumGU) subtype had the highest frequency of pathologic carcinoma in situ (CIS; six/16 [38%] of T1-LumGU vs 13/73 [18%] of all samples; Supplementary Table 2) with moderate enrichment in CIS up and down gene sets and a recurrence rate of 25% (four/16) at 24 mo (Fig. 1D, Supplementary Fig. 3A,B, Supplementary methods). Analysis of T1-LumGU using other classifiers identified 14/16 samples (88%) as Lund GU and nine/16 (56%) as consensusMIBC LumU [4]. T1-LumGU tumors had the largest median number of somatic copy number (CN) gains (Fig. 1G; $p = 0.016$, Kruskal test). While inflammation genes were weakly repressed in T1-LumGU tumors, Molecular Signatures Database (MSigDB) C3 E2F1 motifs were enriched (Supplementary Fig. 4), as were hallmark gene sets for E2F targets and G2M checkpoint (area under the curve [AUC] 0.77 and 0.69, Supplementary Fig. 5).

A set of 170 inflammation-related genes was highly expressed in T1-Inflamed (T1-Inflam) tumors (Fig. 1A,D and Supplementary Fig. 3C; AUC 0.91, CERNO test [5]). T1-Inflam tumors had the highest levels of many immune cell types, including cytotoxic lymphocytes and T cells, as well as the highest immune and stromal scores and the lowest tumor purity (Fig. 1F, Supplementary Fig. 6B). Multiple inflammatory hallmarks were enriched, and Myc and E2F target hallmarks were repressed (Fig. 1C, Supplementary Fig. 5). While T1-Inflam tumors were mostly LumP (11/14, 79%), CIS rates were low (three/14, 21%) and there were four/14 (29%) recurrences by 24 mo. Hallmarks and immune signatures were consistent with increased expression of immune regulators NFATC2 and STAT4 (Supplementary Fig. 4B), and we hypothesize that T1-Inflam tumors represent an immune-active and inflamed T1 subtype.

Collectively, subtypes T1-Myc and T1-Early (S5) had the most recurrences, with over half of tumors recurring after BCG treatment (14/24, 58% of patients at 24 mo over both subtypes; Fig. 1B). T1-Myc had the most recurrences by 24 mo (12/17, 71%). T1-Myc tumors were mostly (14/17, 82%) LumP, and all were UROMOL class 2a. They had high MYC expression levels and enriched Myc target hallmarks (AUC 0.71; Fig. 1C,H and Supplementary Fig. 5). Inflammatory gene signatures were minimally repressed (AUC 0.66, Supplementary Fig. 3C). Pathological CIS was present in two/17 (12%), but CIS gene sets were not enriched (Supplementary Fig. 3A).

Subtype T1-True Luminals (T1-TLum) was the most luminal and urothelial-differentiated subtype. Overall, T1-TLum tumors had the fewest 24-mo recurrences (two/13, 15%). The T1-TLum group had the highest median consensusMIBC LumP classifier score (Fig. 1E) and contained four/13 (31%) UROMOL class 1 tumors. T1-TLum tumors had the fewest somatic CN gains [6] (Fig. 1G) and had strongly repressed CIS (ie, enriched in CIS down with repressed CIS up genes; Supplementary Fig. 3A). Inflammatory and proliferative hallmarks were repressed (Fig. 1C and Supplementary Fig. 5), immune cell markers were low according to multiple deconvolution methods (Supplementary Fig. 6), and luminal differentiation genes FGFR3 and RXRA were highly expressed (Fig. 1H).

Subtype T1-Early had five/13 (38%) recurrences within 6 mo of induction BCG, with no further recurrences by 24 mo. This subtype had the highest median MYC expression and enriched Myc target hallmarks (AUC 0.80; Fig. 1C,H and Supplementary Fig. 5). These tumors had no reported CIS, and had repressed CIS gene signatures (Supplementary Fig. 3). While both T1-Myc and T1-Early had elevated MYC expression, T1-Early differed from T1-Myc in having repressed immune response hallmarks for IFN-α (AUC 0.81) and IFN-γ (AUC 0.75) (Supplementary Fig. 5). Thus, T1-Early appeared to be a MYC-driven subtype with an immune-suppressive microenvironment that was depleted in immune cells, suggesting its tumor microenvironment may represent an immune desert. Grouping the two Myc-driven subtypes together, T1-Early and T1-Myc had significantly worse recurrence-free survival than the other three subtypes grouped ($p = 0.025$, Fig. 1I).

We used regulon analysis to further characterize the molecular differences and similarities among the subtypes. This identified two major patterns of regulon activity that suggested that the five expression subtypes could be grouped into two regulon classes: T1-LumGU + T1-Myc and T1-TLum + T1-Early (Supplementary Fig. 7A). Subtypes T1-LumGU + T1-Myc had activated regulons for transcription factors E2F1 and FOXM1, and enriched hallmarks for E2F targets, G2M checkpoint, and interferon response pathways. By contrast, subtypes T1-TLum + T1-Early (and to some degree T1-Inflam) were characterized by activated

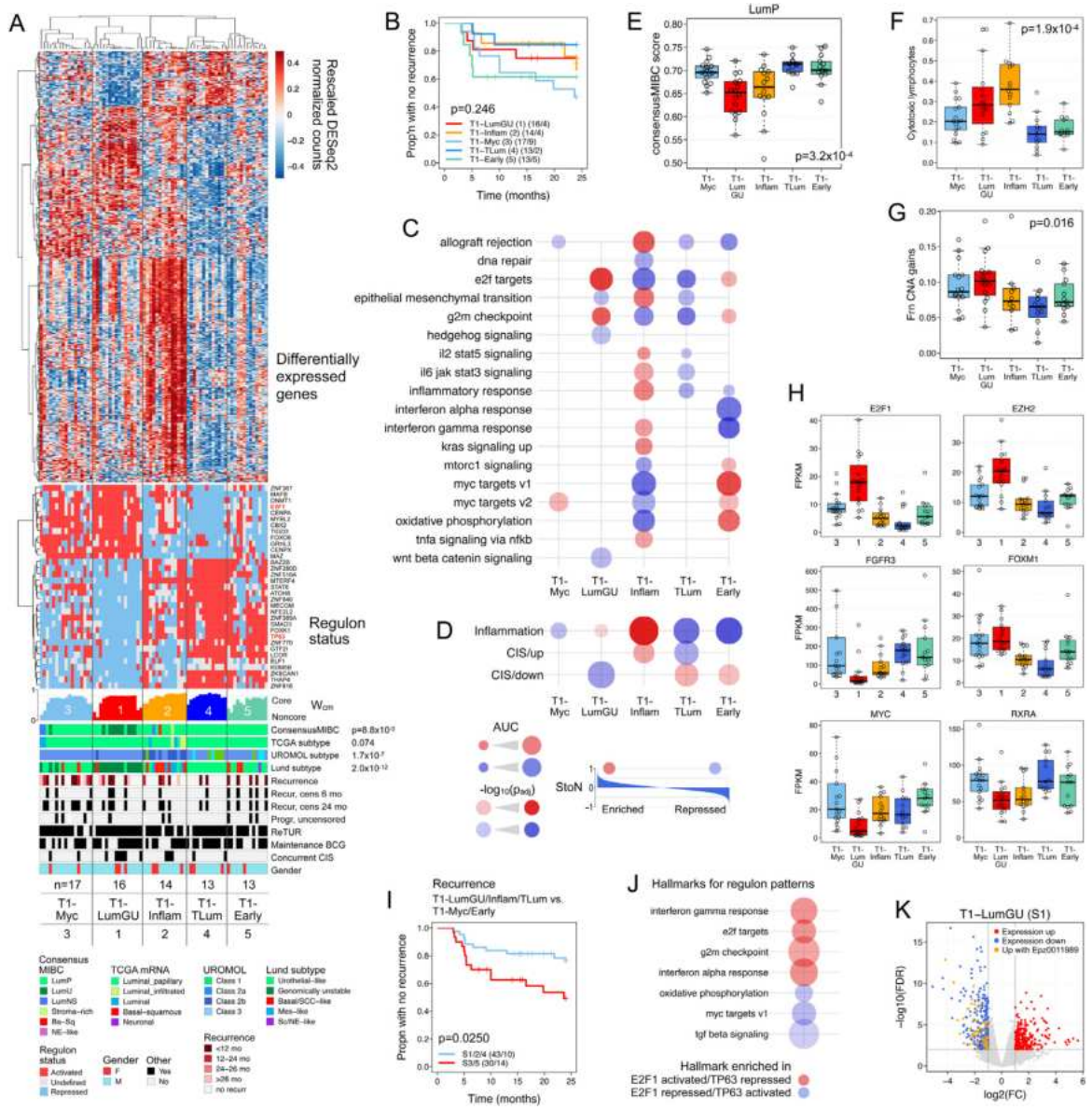
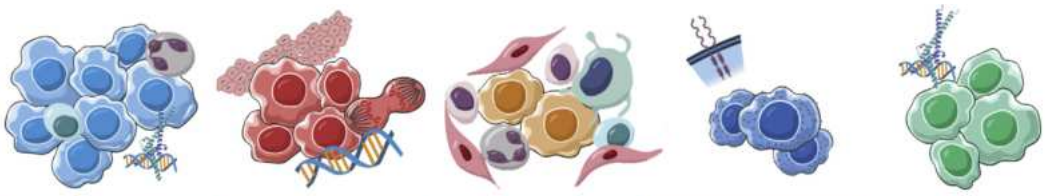


Fig. 1 – Characterization of five gene expression subtypes for T1 tumors based on transcriptome profiles and clinical variables. (A) Top: heatmap of subtype-specific differentially expressed genes (DEGs) for five unsupervised consensus expression clusters identified using the most-variant 2945 (ie, 15%) protein-coding genes (Supplementary methods). Below the DEG heatmap is a heatmap showing activity status profiles for 33 regulons, with red, blue, and grey indicating activated, repressed, and undefined regulon activity status, respectively. Below this are covariate tracks for expression-based classifier subtyping of each T1 tumor, with consensusMIBC, TCGA, UROMOL, and Lund subtypes shown. Below these are clinical and pathologic covariates. (B) Kaplan-Meier plot of recurrence, censored at 24 mo, with a log-rank *p* value, demonstrating increased recurrence of subtypes T1-Myc (S3, 24 mo) and T1-Early (S5, 6 mo). (C) Selected Molecular Signatures Database hallmark gene sets enriched in genes overexpressed (red disks) or underexpressed (blue) in a subtype. Gene set enrichment analysis results are from CERNO tests [5]; disk diameter is proportional to area under the curve (ie, effect size) and color opacity is proportional to $-\log10(p_{Adj})$. (D) CERNO tests of 170 inflammation-related genes and CIS up/down genes, with dot size and color as described in (C). (E) Distribution of LumP consensusMIBC classifier scores across T1 subtypes; T1-TLum had the highest median LumP score. (F) Cytotoxic lymphocytes predicted by MCPcounter (Supplementary Fig. 6); T1-Inflam had the most immune cells. (G) Somatic copy number (CN) gains, expressed as a fraction of the total genome length with CN calls; T1-LumGU had the most CNAs and T1-TLum the fewest. (H) Per-subtype expression distributions of select genes. A comparison of FPKM and TPM expression distributions is shown in Supplementary Figure 4B. (I) A Kaplan-Meier curve identified significantly worse recurrence at 24 mo for the two subtypes with the highest recurrence (T1-Myc and T1-Early) compared to the three other subtypes (T1-LumGU, T1-Inflam, T1-TLum). (J) The regulon-based group consisting of subtypes T1-LumGU + T1-Myc was enriched in hallmarks for E2F targets, G2M checkpoint, and interferon response pathways; by contrast, the group consisting of subtypes T1-TLum + T1-Early (and to some degree T1-Inflam) was characterized by activated SMAD3 and TP63 regulons, and enriched in hallmarks for TGF-β signaling, MYC targets, and oxidative phosphorylation (Supplementary Fig. 9). (K) Differentially expressed genes were identified for T1-LumGU; overexpressed genes are shown by red dots and underexpressed by blue dots (Supplementary Fig. 10). This subtype had gene signatures suggestive of regulation by E2F and EZH2. Treatment of bladder cancer cell line HT-1376 with EPZ0011989 (Epizyme, Cambridge, MA, USA) resulted in increased expression of many of the repressed genes, depicted by orange dots, suggesting that subtype-specific genes may be regulated by EZH2. FC = fold change. The *p* values in A are from Fisher exact tests on contingency tables; those in E, F, and G are from Kruskal-Wallis tests on per-subtype FPKM distributions; all are uncorrected for multiple testing.

Table 1 – Characteristics of the five expression subtypes in the discovery cohort.



Subtype name (number)	T1-Myc (3)	T1-LumGU (1)	T1-Inflam (2)	T1-TLum (4)	T1-Early (5)
Samples (n)	17	16	14	13	13
Subtype classifiers					
Lund	URO	GU	URO, some Basal/ SCC-like, Mes-like	URO	URO
TCGA mRNA	Lum-papillary	Lum-papillary	Lum-papillary	Lum-papillary	Lum-papillary
consensusMIBC	LumP	LumU	LumP/Stroma-rich	LumP	LumP
UROMOL class	2a	2a	2a/2b	1/2a	2a/3
Hallmark gene sets					
Enriched		E2F targets, G2M checkpoint	Inflammatory response, IL2/STAT5 signaling, IFNG response		MYC targets v1
Repressed			MYC targets v1, E2F targets, G2M checkpoint	E2F targets G2M checkpoint	IFNG response IFNA response
Carcinoma in situ					
Pathologic (%)	12	38	21	15	0
GSEA		Moderate	Moderate	Strongly repressed	Weakly repressed
GSEA inflammation			Strongly enriched	Strongly repressed	Strongly repressed
Immune: MCPcounter					
CTLs			Highest	Lowest	Low
T cells			Highest median	Lowest	Lowest median
B lineage				Lowest median	Low
Immune: ESTIMATE					
Immune score	Low, wide range	Moderate, wide range	Highest	Low	Lowest median
Stromal score	Low	Low	Highest	Lowest median	Low
Tumor purity	High	High	Lowest	High	High
Gene expression	High FOXM1, RXRA Wide range for MYC	High E2F1, EZH2 Lowest FGFR3, MYC	High STAT4, NFATC2	Low E2F1, FOXM1, NFATC2, STAT4	High MYC, Low STAT4
CN somatic gains		Highest	Low	Lowest	Low
Activated regulons	Moderate E2F1	E2F1 set	TP63/ZNF385A	ZNF385A (TP63)	Moderate ZNF385A
BCG response					
Recurrence, 6 mo	3/17 (18%)	3/16 (19%)	1/14 (7%)	1/13 (8%)	5/13 (38%)
Recurrence, 24 mo	12/17 (53%)	4/16 (25%)	4/14 (29%)	2/13 (15%)	5/13 (38%)
Management	Early cystectomy, MYC-i	BCG, EZH2i	BCG	TURBT, BCG	Nadofaragene firadenovec, MYC-i

BCG = bacillus Calmette-Guerin; CN = copy number; CTLs = cytotoxic T lymphocytes; GSEA = gene set enrichment analysis; TURBT = transurethral resection of bladder tumor

SMAD3 and TP63 regulons, and enriched hallmarks for TGF-β signaling, MYC targets, and oxidative phosphorylation (Fig. 1J and Supplementary Fig. 7B). We found that these two major patterns of regulon activity were also present in a cohort of 94 UROMOL T1 non-cystectomy tumors; these patterns were consistent with classifier subtyping and with relative expression levels of E2F1 and other genes [7] (Supplementary Fig. 8). That the five expression subtypes corresponded to two major regulon activity classes suggests that regulon activity profiles may provide coarser-grained groupings for T1 tumors.

So that we could evaluate our subtypes in other patient cohorts, we developed an expression-based single-sample classifier for T1 tumors (https://github.com/csgroen/classifyT1BC). Since our discovery cohort was restricted to tumors treated with BCG, we evaluated tumors from a second cohort of 26 T1 patients from our institution whose tumors had all been T1 on TUR but who elected to undergo early cystectomy rather than BCG treatment (Supplementary Table 1B, Supplementary Fig. 9). The classifier identified the five T1 subtypes in the 26 tumors. As validation of the classifier, we identified conserved regulon activity patterns, relative levels of gene expression, tumor subtypes, and pathologic CIS in the predicted subtypes (Supplementary Fig. 9E). This result was consistent with the UROMOL results (Supplementary Fig. 8) and showed that gene expression and regulons active within our five T1 subtypes were conserved in another cohort of T1 tumors, despite differences in outcomes, sample preparation, and treatment.

One potential application of T1 subtypes is to direct precision therapy targeting the unique features of a patient's subtype. T1-LumGU tumors had the highest expression of E2F and its target EZH2. In a test of EZH2

as a potential target in bladder cancer, we found that in vitro treatment of the luminal bladder cancer cell line HT-1376 with an EZH2 inhibitor (EPZ-011989, a generous gift from Epizyme) strongly enhanced expression of DEGs that were repressed or underexpressed in T1-LumGU (Supplementary Fig. 10 and Fig. 1K). While preliminary, these data suggest that consideration of the unique expression signature of each subtype and/or its regulon network may identify novel therapeutic targets for T1 tumors.

In summary, using a cohort of patients with T1 NMIBC treated with BCG, we identified five distinct molecular subtypes that appeared to be associated with two major classes of regulon activity, and we describe the characteristics of each subtype. In the future, evaluation of T1 subtypes may help to risk-stratify T1 tumors and identify precision therapeutic targets.

Author contributions: Joshua J. Meeks had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Robertson, Meeks, Jordan, Lin, McLaughlin, Das, Fall, Taxter, Dyrskjøt, McConkey, Svatek, Castro, Fantini, Groeneveld, de Reyniès.
Acquisition of data: Robertson, Meeks, Jordan, Lin, McLaughlin, Das, Fall, Taxter, Dyrskjøt, McConkey, Svatek, Castro, Mogil, Viborg Lindskrog, Fantini.
Analysis and interpretation of data: Robertson, Meeks, Jordan, Lin, McLaughlin, Das, Fall, Taxter, Dyrskjøt, McConkey, Svatek, Castro, Mogil, Viborg Lindskrog, Fantini, Mogil, Groeneveld, de Reyniès.
Drafting of the manuscript: Robertson, Meeks, Jordan, Lin, McLaughlin, Das, Fall, Taxter, Dyrskjøt, McConkey, Svatek, Castro, Mogil, Viborg Lindskrog, Fantini, Mogil, Groeneveld, de Reyniès.
Critical revision of the manuscript for important intellectual content: Robertson, Meeks, Jordan, Lin, McLaughlin, Das, Fall, Taxter, Dyrskjøt, McConkey, Svatek, Castro, Mogil, Viborg Lindskrog, Fantini, Mogil, Groeneveld, de Reyniès.
Statistical analysis: Robertson, Meeks, Jordan, McLaughlin, Das, Taxter, Castro, Mogil, Viborg Lindskrog, Fantini, Groeneveld, de Reyniès.
Obtaining funding: Meeks, Svatek, McConkey.
Administrative, technical, or material support: None.
Supervision: Meeks, Svatek, Robertson, Dyrskjøt, Robertson, de Reyniès.
Other: None.

Financial disclosures: Joshua J. Meeks certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Joshua J. Meeks is a consultant for Ferring, AstraZeneca, and Janssen and has participated in advisory boards for Foundation Medicine and Nucleix. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: Joshua J. Meeks is supported by grants from VHA (BX003692-01), DoD (W81XWH-18-0257), the Dixon Foundation, and a HOPE Foundation SEED award. The sponsors played a role in the design and conduct of the study.

Acknowledgments: We gratefully acknowledge Mao Miyamoto for contributing the illustrations for Table 1, and Epizyme (Cambridge MA) for contributing the EZH2 inhibitor EPZ-011989.

Data availability: RNA-seq and clinical data are available at the Gene Expression Omnibus as GSE154261.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.048.

References

[1] van den Bosch S, Witjes JA. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. Eur Urol 2011;60:493–500.
[2] Meeks JJ, Carneiro BA, Pai SG, et al. Genomic characterization of high-risk non-muscle invasive bladder cancer. Oncotarget 2016;7:75176–84.
[3] Pennock ND, Jindal S, Horton W, et al. RNA-seq from archival FFPE breast cancer samples: molecular pathway fidelity and novel discovery. BMC Med Genomics 2019;12:195.
[4] Kamoun A, de Reyniès A, Allory Y, et al. A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol 2020;77:420–33.
[5] Zyla J, Marczyk M, Domaszewska T, Kaufmann SHE, Polanska J, Weiner J. Gene set enrichment for reproducible science: comparison of CERNO and eight other algorithms. Bioinformatics 2019;35:5146–54.
[6] Beaubier N, Bontrager M, Huether R, et al. Integrated genomic profiling expands clinical options for patients with cancer. Nat Biotechnol 2019;37:1351–60.
[7] Hedegaard J, Lamy P, Nordentoft I, et al. Comprehensive transcriptional analysis of early-stage urothelial carcinoma. Cancer Cell 2016;30:27–42.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 533–537 of this issue

Molecular Subtypes of T1 Bladder Cancer: Biomolecular Characteristics Versus Clinical Utility

Douglas G. Ward, Roland Arnold, Richard T. Bryan *

Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

From low-grade Ta to high-grade T1, Non–Muscle-Invasive Bladder Cancers (NMIBCs) are highly heterogeneous both clinically and biologically. As with Muscle-Invasive Bladder Cancer (MIBC), high-grade NMIBCs have a high mutation burden, multiple copy-number changes, and loss of tumour suppressors (eg, TP53, RB1), whereas low-grade NMIBCs exhibit oncogene activation (eg, FGFR3, RAS) in a relatively normal genome [1]. Subtyping based on gene expression has recently offered further insights into NMIBC biology [1–3], yet risk stratification (and hence treatment selection) remains entirely based on clinicopathological observations, without the inclusion of biomolecular information [4].

The majority of urologists treat patients with high-grade T1 disease with induction and maintenance intravesical Bacillus Calmette-Guérin (BCG), with radical cystectomy considered for suitable patients [4]. BCG efficacy varies: more than 60% of patients experience durable responses [5,6], up to 20% experience progression to MIBC within 5 yr [5,6], and as many as 15% have lymph node metastases at diagnosis [7]. There would be great benefit to patients if biomolecular insights could be used to predict those more likely to respond to BCG, those who should be treated with other (novel) therapeutics, those who would be optimally managed with early radical cystectomy, and, potentially, those who do not require prolonged adjuvant therapies.

In this issue of European Urology, Robertson et al [8] describe the identification of five subtypes of high-grade T1 bladder cancer. The authors used a discovery cohort of 73 patients with high-grade T1 disease; 84% of these patients had undergone repeat Transurethral Resection (TUR), 100% had received induction BCG, and 64% had received maintenance BCG. At 24 mo, 32% had recurred and 8% had progressed to MIBC; overall, nine patients progressed during follow-up. TUR specimens were subjected to RNA sequencing using standard methodology. State-of-the-art analyses were used to interpret the data at the level of defined pathways and regulons, and to provide insights into the (immune) microenvironment.

In brief, unsupervised consensus clustering based on gene expression was used to define five subtypes considered to optimally describe tumour biology and characteristics, with an open-access "single sample classifier" generated to facilitate subtyping. Regulon analysis identified a dichotomy, with similar transcription factor activity in the T1-Myc and T1-LumGU subtypes and in the T1-TLum and T1-Early subtypes. Although recurrence-free survival curves for the five subtypes did not differ significantly, there was a significant difference in recurrence-free survival between combined T1-Myc/Early and combined T1-LumGU/Inflam/TLum. As a limited validation, the gene expression patterns were corroborated in a cohort of 26 patients with high-grade tumours who underwent radical cystectomy (69% $\leq$T1, 31% $\geq$T2), suggesting that the five subtypes are intrinsic properties of high-grade bladder cancer rather than a result of "overfitting". Subsequent in vitro data highlighted the potential of this classification for the selection of targeted therapies.

Unlike previous studies predominantly focussed on MIBCs and/or NMIBCs of all grades and stages [2,3,9], the current study has the advantage that it analysed only high-grade T1 tumours from patients treated with at least induction BCG; hence, the influence of intrinsic biology on the outcomes of high-grade T1 disease can largely be separated from the confounding effects of grade, stage, and varying treatments (see later). Comparison with existing subtyping methods showed that T1-LumGU shows similar-

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.048.
* Corresponding author.The Bladder Cancer Group, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT,UK.

https://doi.org/10.1016/j.eururo.2020.07.021

ity to LumU (MIBC consensus [9]) and GU (Lund [2]) subtypes, and T1-Inflam shows similarity to cluster 2b (UROMOL [10]) and Basal and Mesenchymal (Lund) subtypes, whilst the remaining proposed T1 subtypes are predominantly similar to LumP (MIBC consensus), cluster 2a (UROMOL) and urothelial-like (Lund). Thus, the subtypes described here provide more detailed characterisation of T1 tumours than existing schema.

The Brief Correspondence format does not do justice to these data, nor permit detailed explanations of methodology and iterative steps. Hence, the analyses are not without the need for clarification and, as the authors state, the results require robust independent validation. Although high MYC expression is a reason to combine T1-Myc and T1-Early (with a significant recurrence-free survival difference vs T1-LumGU/Inflam/TLum), these are derived from opposite regulon clusters, and other shared biology is not evidenced. In addition, data relating to the immune microenvironment should be interpreted carefully: for example, MCP-counter does not report absolute measurements of cell-type fractions but individual cell-type scores, which are potentially influenced by normalisation procedures. Furthermore, it remains unclear if the validation readout (expression of two regulons, expression of seven genes, CIS gene-set expression, and MIBC subtype) is not intrinsically modelled in the classifier (which is based on the expression of 300 genes). In addition, the differential outcomes for the subtypes are based on a small number of events in a modest number of patients with no independent validation. Finally, is recurrence-free survival the most clinically relevant outcome for patients with high-grade T1 tumours following induction BCG? Figure 1A [8] illustrates the treatments for the nine patients who progressed to MIBC: only one patient had undergone both repeat TUR and received maintenance BCG. Progression in patients with high-grade T1 disease after optimal bladder-preserving management (repeat TUR, induction and maintenance BCG [4]) is life-threatening, and is the outcome of most interest to clinicians (and their patients). Arguably, this one patient is the only patient who matters in this study: what are the unique biomolecular characteristics of her tumour?

As with interventional clinical trials in which sample size calculations are undertaken to adequately "power" the study, it is likely that many hundreds of T1 tumours (accompanied by high-quality clinical data and follow-up) need to be analysed to answer the question(s) of most importance for this clinical setting. With RNA sequencing still costly and transcriptome data analysis complex, this remains a challenge. In addition, subtype is only one of the biomolecular factors influencing outcomes for high-grade T1 disease, with important contributions to pathogenesis from other genomic and epigenomic phenomena, as well as cell and immune biology. There is still a long journey ahead to fully understand high-grade T1 disease so that we can optimally stratify patients and develop new therapies; however, alongside previous analyses [1–3,10], this study represents a promising waypoint.

Conflicts of interest: Richard T. Bryan has contributed to advisory boards for Olympus Medical Systems and Janssen, and undertakes research funded by UroGen Pharma. Douglas G. Ward and Roland Arnold have nothing to disclose.

References

[1] Hurst CD, Platt F, Taylor CF, Knowles MA. Novel tumor subgroups of urothelial carcinoma of the bladder defined by integrated genomic analysis. Clin Cancer Res 2012;18:5865–77.

[2] Sjodahl G, Lauss M, Lovgren K, et al. A molecular taxonomy for urothelial carcinoma. Clin Cancer Res 2012;18:3377–86.

[3] Hedegaard J, Lamy P, Nordentoft I, et al. Comprehensive transcriptional analysis of early-stage urothelial carcinoma. Cancer Cell 2016;30:27–42.

[4] Babjuk M, Burger M, Comperat EM, et al. European Association of Urology guidelines on non–muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. Eur Urol (76):2019;639–57.

[5] Thomas F, Noon AP, Rubin N, Goepel JR, Catto JW. Comparative outcomes of primary, recurrent, and progressive high-risk non-muscle-invasive bladder cancer. Eur Urol 2013;63:145–54.

[6] Martinez-Pineiro L, Portillo JA, Fernandez JM, et al. Maintenance therapy with 3-monthly bacillus Calmette-Guerin for 3 years is not superior to standard induction therapy in high-risk non-muscle-invasive urothelial bladder carcinoma: final results of randomised CUETO study 98013. Eur Urol 2015;68:256–62.

[7] Wiesner C, Thomas C, Salzer A, Gillitzer R, Hampel C, Thuroff JW. [Prevalence of lymph node metastases in non-muscle-invasive bladder cancer. Delay of radical cystectomy and upstaging in the cystectomy specimen as risk factors]. Urologe A 2008;47:1162–6.

[8] Robertson AG, Groeneveld CS, Jordan B, et al. Identification of differential tumor subtypes of T1 bladder cancer.. Eur Urol 2020;78:533–7.

[9] Kamoun A, de Reyniès A, Allory Y, et al. A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol 2020;77:420–33.

[10] Lindskrog S.V., Prip F.F., Lamy P., et al. An integrated multi-omics analysis identifies clinically relevant molecular subtypes of non-muscle-invasive bladder cancer. medRxiv In press. 10.1101/2020.06.19.20054809.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Brief Correspondence

Editorial by Vancheswaran Gopalakrishnan, Bret R. Sellman, Taylor S. Cohen and Phillip A. Dennis on pp. 544–545 of this issue

Concomitant Antibiotic Use and Survival in Urothelial Carcinoma Treated with Atezolizumab

Ashley M. Hopkins [a,*], *Ganessan Kichenadasse* [a,b], *Christos S. Karapetis* [a,b], *Andrew Rowland* [a,†], *Michael J. Sorich* [a,†]

[a] *College of Medicine and Public Health, Flinders University, Adelaide, Australia;* [b] *Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Flinders Medical Centre, Adelaide, Australia*

Article info

Article history:
Accepted June 29, 2020

Associate Editor:
James Catto

Stats Editor:
Andrew Vickers

Keywords:
Urothelial carcinoma
Atezolizumab
Immune checkpoint inhibitors
Antibiotics
Survival

Abstract

Antibiotic effects on the gut microbiota may negatively impact survival with immune checkpoint inhibitors (ICIs). However, there is minimal evidence regarding whether antibiotic impacts are specific to ICIs or impacts in urothelial carcinoma (UC). In a post hoc analysis of IMvigor210 (single-arm atezolizumab) and IMvigor211 (phase III randomised trial of atezolizumab vs chemotherapy), the association between antibiotic use and overall survival (OS) and progression-free survival (PFS) was assessed via Cox proportional hazard analysis. Antibiotic use was defined as any antibiotic administration between 30 d prior to and 30 d after treatment initiation. Antibiotic use was associated with worse OS ($n = 847$, hazard ratio or HR [95% confidence interval {CI}] = 1.44 [1.19–1.73]) and PFS (1.24 [1.05–1.46]) with atezolizumab, but not chemotherapy ($n = 415$, 1.15 [0.91–1.46] and 1.09 [0.88–1.36], respectively). In the randomised cohort of IMvigor211, the OS treatment effect (HR [95% CI]) of atezolizumab versus chemotherapy was 0.95 (95% CI 0.71–1.25) for antibiotic users, compared with 0.73 (0.60–0.88) for nonusers (p[interaction] = 0.1). Similar associations were noted in the PD-L1 IC2/3 population. In conclusion, antibiotic use was associated with worse survival outcomes in UC patients treated with atezolizumab. The study does not justify a change in antibiotic selection for infections; however antibiotic overuse occurs in cancer care and this needs to be evaluated for ICIs.

Patient summary: In this report from clinical trials IMvigor210 and IMvigor211, it was demonstrated that antibiotic use is consistently associated with worse survival in patients with urothelial carcinoma treated with atezolizumab. No antibiotic association was observed in patients treated with chemotherapy, suggesting that antibiotics may specifically reduce the effectiveness of cancer immunotherapies. Future research will continue to explore the effect of antibiotics on other immune checkpoint inhibitors and confirm whether immune checkpoint inhibitors remain the treatment of choice in cancer patients requiring antibiotics.

† Professor Sorich and Associate Professor Rowland contributed equally to this study.
* Corresponding author. College of Medicine and Public Health, Flinders University, Adelaide SA 5042, Australia. Tel.: +61 8 8201 5647.
E-mail address: ashley.hopkins@flinders.edu.au (A.M. Hopkins).

https://doi.org/10.1016/j.eururo.2020.06.061
0302-2838/

The gut microbiota plays an important role in regulating homoeostasis and immune function, and there is evidence that an altered gut microbiota can impact systemic immune response and immune checkpoint inhibitor (ICI) efficacy negatively [1–3]. Antibiotics cause significant changes to the gut microbiota, including decreased diversity and abundance of bacteria in the gut, and these changes can be long lasting [4,5]. Hypotheses are that antibiotic use may also impact survival outcomes from ICIs negatively [6–8]. The effects of antibiotics on ICIs used in urothelial carcinoma (UC) treatment have not been assessed. Additionally, there is minimal evidence to indicate whether the effect of antibiotics is specific to ICIs or if they impact other treatments more broadly.

This manuscript presents a post hoc analysis of the locally advanced/metastatic UC trials, IMvigor210 (NCT02108652; July 4, 2016 cut-off) [9,10] and IMvigor211 (NCT02302807; March 13, 2017 cut-off) [11]—pivotal trials in the assessment of atezolizumab for UC treatment. The primary aim of this manuscript was to assess the association between antibiotic use (within a period between 30 d prior to and 30 d after treatment initiation) and overall survival (OS) and progression-free survival (PFS). This time frame was analysed based upon prior analyses [6,7] and the evidence that antibiotic therapy can result in a prolonged impact on the gut microbiota, including from short courses [4,5].

In brief, IMvigor211 was a randomised trial of atezolizumab (1200 mg intravenous [IV] every 3 wk) versus docetaxel (75 mg/m^2 IV every 3 wk), paclitaxel (175 mg/m^2 IV every 3 wk), or vinflunine (320 mg/m^2 IV every 3 wk) for patients with locally advanced/metastatic UC who have progressed during or following a prior platinum-based chemotherapy regimen [11]. IMvigor210 was a single-arm study of atezolizumab 1200 mg IV every 3 wk in locally advanced or metastatic UC, including participants who were both treatment naïve and ineligible for cisplatin-containing chemotherapy, or participants who have progressed during or following a prior platinum-based chemotherapy regimen [9,10]. Primary study definitions of OS and PFS were utilised in this manuscript [9–11]. PFS was assessed by an investigator as per the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) in IMvigor211 and by an independent review facility as per RECIST (version 1.1) in IMvigor210.

Associations between antibiotic use and OS/PFS were modelled using Cox proportional hazard regression. Analyses were adjusted for baseline age, sex, body mass index, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, histology, count of prior treatments, PD-L1 expression (expression on $<$1% [IC0] or 1–$<$5% [IC1] or $\geq$5% of tumour-infiltrating immune cells [IC2/3]) [9–11], serum haemoglobin levels, count of organ sites with metastases, and presence of liver metastases. Pooled analyses were stratified by study. Prognostic association heterogeneity between studies was assessed using a study-by-treatment interaction term in the Cox proportional regression model. Heterogeneity of antibiotic effect size for atezolizumab versus chemotherapy in the randomised arms of IMvigor211 was assessed using an antibiotic-by-treatment interaction term. Associations were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs) and p values (likelihood ratio test). Kaplan-Meier analysis was used for estimating and plotting survival probabilities. Statistical analyses were performed using R version 3.4.3.

Within IMvigor210, 112 (26%) of 429 participants initiated on atezolizumab received an antibiotic within the 60-d window. Of the 467 participants, 123 (26%) randomised to atezolizumab and 149 (32%) randomised to chemotherapy received an antibiotic in IMvigor211. Median (interquartile range) follow-up for patients without the event was 11 (8–12) and 16 (14–19) mo in IMvigor210 and IMvigor211, respectively. At data cut-off, 239 of the 429 participants in IMvigor210 had died (342 PFS events), and 674 of the 931 participants in IMvigor211 had died (817 PFS events). Supplementary Table 1 presents patient characteristics by antibiotic use status; of note, antibiotic users had higher ECOG PS (p = 0.008) and lower haemoglobin (p = 0.01).

In patients treated with atezolizumab in the pooled cohort of IMvigor210 and IMvigor211, antibiotic use was associated with significantly worse OS (HR [95% CI] = 1.44 [1.19–1.73]) and PFS (1.24 [1.05–1.46]; Fig. 1 and Supplementary Fig. 1). No significant heterogeneity was observed in the antibiotic association between studies (OS p[interaction] = 0.9; PFS p[interaction] = 0.5). In patients treated with chemotherapy in IMvigor211, no significant association between antibiotic use and OS (HR [95% CI] = 1.15 [0.91–1.46]) or PFS (1.09 [0.88–1.36]) was observed (Fig. 1 and Supplementary Fig. 1).

In the total randomised cohort of IMvigor211, the OS treatment effect (HR [95% CI]) of atezolizumab vs chemotherapy was 0.95 (0.71–1.25) for antibiotic users, compared with 0.73 (0.60–0.88) for antibiotic nonusers (p[interaction] = 0.1; Supplementary Fig. 2). On sensitivity analysis of the PD-L1 IC2/3 population, the OS treatment effect of atezolizumab versus chemotherapy was 0.91 (0.52–1.57) for antibiotic users, compared with 0.56 (0.39–0.81) for antibiotic nonusers (p[interaction] = 0.2; Supplementary Fig. 2).

A significant strength of this study is the availability of data from the randomly allocated chemotherapy arms of IMvigor211, allowing valid inferences of treatment effect. Our findings are similar to those of Chalabi et al [7] who identified a significant negative prognostic association of antibiotic use on OS in advanced non–small-cell lung cancer treated with atezolizumab, with no significant association for docetaxel. While both this study and the prior study by Chalabi et al [7] were underpowered to detect a statistically significant treatment-by-covariate interaction, the consistency in findings exemplifies an urgent need for a comprehensive pooled analysis of all ICI randomised clinical trials to determine conclusively whether antibiotics influence ICI efficacy or they are simply a prognostic marker for many treatments. This cannot be determined from single-arm studies or unmatched observational studies, for which inferences are strongly confounded by the indication of antibiotic therapy [6,12].

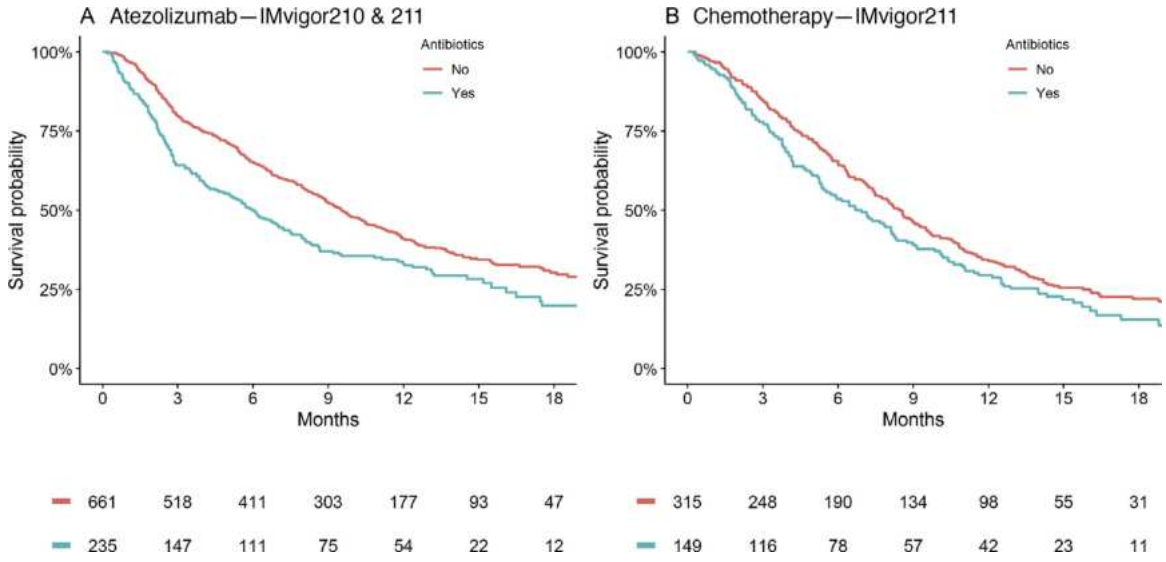


Fig. 1 – Kaplan–Meier estimates of OS by antibiotic use status for participants randomised to (A) atezolizumab or (B) chemotherapy within IMvigor211 and IMvigor210. OS = overall survival.

This study pooled large, high-quality data from two contemporary trials, increasing power and generalisability. The study was limited in its ability to provide evidence on the effect of antibiotic duration, type, or indication (see the Supplementary material), which needs to continue to be explored. For example, emerging evidence links UC to higher incidences of urinary tract infections (UTIs) and recurrent UTIs to increased risks of UC [13]. This study is the first to provide evidence that antibiotics, which impact the gut microbiota, have substantial associations with outcomes for ICIs used in UC [6,14]. Antibiotic effects on the urinary microbiota may also be important [15]. A limitation of this study is the restricted range of ICIs and settings evaluated. Future research should expand the range of ICIs and cancer types evaluated.

In conclusion, antibiotic use was demonstrated as independently associated with worse survival outcomes in locally advanced/metastatic UC treated with atezolizumab. The adverse prognostic effect of antibiotics was not observed to be statistically significant in patients randomised to chemotherapy, suggesting that antibiotics may influence the magnitude of ICI efficacy. This post hoc analysis does not justify a change in antibiotic selection for bacterial infections, as these infections need to continue to be treated properly. However, research indicates that overuse of antibiotics in cancer care occurs [16], and in addition to increasing potential risks of resistant bacterial infections, this study's findings suggest a need for extra caution when an ICI is being used. In addition, this study provides strong justification for prospective studies to tease out whether antibiotics are primarily a surrogate of an unfit or immunodeficient patient or whether antibiotic effects on the gut microbiota are having casual impacts on ICI efficacy. If the latter is true, in patients at a high risk of recurrent infections, it may need to be considered whether ICI therapy is most appropriate.

A secondary analysis of anonymised clinical trial data was confirmed negligible risk research by the Southern Adelaide Local Health Network, Office for Research and Ethics, and was exempt from review.

Data were accessed according to Roche's policy and process for clinical study data sharing at https://clinicalstudydatarequest.com/.

Author contributions: Ashley M. Hopkins had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Acquisition of data: Hopkins, Rowland, Sorich.
Analysis and interpretation of data: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Drafting of the manuscript: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Critical revision of the manuscript for important intellectual content: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Statistical analysis: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Obtaining funding: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Administrative, technical, or material support: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Supervision: Hopkins, Kichenadasse, Karapetis, Rowland, Sorich.
Other: None.

Financial disclosures: Ashley M. Hopkins certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Michael J. Sorich and Andrew Rowland report investigator-initiated project grants from Pfizer, outside the submitted work. Christos S. Karapetis reports advisory board roles with AstraZeneca, Merck Sharp & Dohme, Bristol-Myers Squibb, and Roche, outside the submitted work. Ganessan Kichenadasse and Ashley M. Hopkins have no conflicts of interest to disclose.

***Funding/Support and role of the sponsor*:** Michael J. Sorich and Andrew Rowland are supported by Beat Cancer Research Fellowships from Cancer Council South Australia. Ashley M. Hopkins is supported by a Postdoctoral Fellowship from the National Breast Cancer Foundation, Australia (PF-17-007). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.061.

References

[1] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91–7.

[2] Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 2018;359:104–8.

[3] Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103.

[4] Abu-Sbeih H, Herrera LN, Tang T, et al. Impact of antibiotic therapy on the development and response to treatment of immune checkpoint inhibitor-mediated diarrhea and colitis. J Immunother Cancer 2019;7:242.

[5] Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. Front Microbiol 2015;6:1543.

[6] Elkrief A, Derosa L, Kroemer G, Zitvogel L, Routy B. The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: a new independent prognostic factor? Ann Oncol 2019;30:1572–9.

[7] Chalabi M, Cardona A, Nagarkar DR, et al. Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: pooled post hoc analyses of the OAK and POPLAR trials. Ann Oncol 2020;31:525–31.

[8] Mohiuddin JJ, Chu B, Facciabene A, et al. Association of antibiotic exposure with survival and toxicity in patients with melanoma receiving immunotherapy. J Natl Cancer Inst 2020. http://dx.doi.org/10.1093/jnci/djaa057.

[9] Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

[10] Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67–76.

[11] Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748–57.

[12] Pinato DJ, Howlett S, Ottaviani D, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. JAMA Oncol 2019;5:1774–8.

[13] Bayne CE, Farah D, Herbst KW, Hsieh MH. Role of urinary tract infection in bladder cancer: a systematic review and meta-analysis. World J Urol 2018;36:1181–90.

[14] Hopkins AM, Rowland A, Kichenadasse G, et al. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. Br J Cancer 2017;117:913–20.

[15] Bersanelli M, Santoni M, Ticinesi A, Buti S. The urinary microbiome and anticancer immunotherapy: the potentially hidden role of unculturable microbes. Target Oncol 2019;14:247–52.

[16] Krantz EM, Zier J, Stohs E, et al. Antibiotic prescribing and respiratory viral testing for acute upper respiratory infections among adult patients at an ambulatory cancer center. Clin Infect Dis 2019;70:1421–8.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 540–543 of this issue

Antibiotics and Immunotherapy: Too Much of Anything is Bad!

Vancheswaran Gopalakrishnan [a,*], *Bret R. Sellman* [a], *Taylor S. Cohen* [a], *Phillip A. Dennis* [b]

[a] *Microbiome Discovery, Microbial Sciences, BioPharmaceuticals R & D, AstraZeneca, Gaithersburg, USA;* [b] *Oncology R & D, AstraZeneca, Gaithersburg, USA*

The gastrointestinal (gut) microbiome has emerged as a key mediator of cancer treatment outcomes, and is seen as having the potential to account for some of the heterogeneity associated with responses to immunotherapy treatment, particularly immune checkpoint blockade therapy (ICB) [1]. Specifically, high diversity and differential abundance of beneficial bacterial taxa in the gut, such as Ruminococcaceae, *Akkermansia* and *Bifidobacterium*, have been reported to be closely linked to positive responses to ICB. Their benefit is conferred through an active and dynamic cross-talk with the immune system leading to enhanced maturation of dendritic cells, increased priming and greater accumulation of effector T-cells in the tumor microenvironment [2–4]. These findings have resulted in a paradigm shift in which the gut microbiome is now being strongly considered as both a predictive biomarker for treatment response, as well as a therapeutic target to maximize the efficacy of immunotherapies. Consequently, there has been a renewed emphasis on antibiotics (abx), which are frequently prescribed during the course of treatment in cancer patients and have a major effect on the composition of the gut microbiome [5].

The link between the gut microbiome and therapeutic efficacy is context-specific and a universal response-associated signature is yet to be identified. Despite this uncertainty, several investigators have reported that indiscriminate abx use impairs the efficacy of immunotherapies in multiple cancers, after accounting for known prognostic markers. A recent meta-analysis lent further credence to these findings by analyzing data from several published studies to confirm that reduced overall (OS) and progression-free survival (PFS) rates were indeed associated with abx usage [6]. There is lack of consensus around timing of abx, with both prior and concurrent use shown to affect efficacy, though administration of broad-spectrum abx prior to start of therapy was recently reported to have a significantly worse impact when compared to concurrent use [7]. Nevertheless, the negative impact of abx is likely mediated by a non-selective disruption of the baseline eubiotic state resulting in skewing of bacterial abundances and reduced overall diversity. These may further lead to metabolic alterations, and a dampening of overall anticancer immunity, by shifting towards an immunosuppressive state that may decrease responsiveness to immune-oncology agents. These changes can be robust and rebounding to the baseline state is unlikely to be achieved in the short-term [8].

In this month's issue of European Urology, Hopkins et al. have added to this body of evidence by analyzing data from two large randomized clinical trials (IMvigor 210 and IMvigor 211) [9]. They report that concomitant abx use; defined as the 60-day interval spanning 30 days prior to and following treatment initiation; was associated with reduced OS in locally advanced/metastatic, cisplatin-refractory urothelial carcinoma patients treated with the anti-PDL-1 monoclonal antibody, Atezolizumab (but not in those treated with chemotherapy). Furthermore, the treatment benefit conferred by Atezolizumab over chemotherapy in terms of OS (but not PFS) was attenuated in the abx-treated group. While this study is timely, and has explored an important clinical issue, several caveats should be considered [9]. The authors themselves are cautious in their interpretation of results. For example, ECOG performance status is generally low in this cohort which may not be representative of a general cancer patient population. Nevertheless, it tended to be higher in patients who were prescribed abx, suggesting poor overall health in this group.

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.061.
* Corresponding author. AstraZeneca, One Medimmune Way, Gaithersburg, MD 20878, USA.
E-mail address: vancheswaran.gopalakrishnan@astrazeneca.com (V. Gopalakrishnan).

https://doi.org/10.1016/j.eururo.2020.07.027

Lack of information on the impact of abx classes seems to be a missed opportunity, especially given the relatively large sample size, and the fact that abx that target predominantly gram-positive or gram-negative bacteria may have differential predictive value for response to ICB. Along these lines, it is also quite surprising that extended abx use (beyond 9 days) and use of more than one class of abx, which could be presumed to lead to more sustained dysbiosis, did not impact OS [9].

It is also important to note that some studies have found no association between abx use and response to ICB [10], and findings from observational cohorts may be confounded by overall health status of patients that necessitates abx use. As such, these data have continued to polarize opinions regarding the impact of abx in cancer patients, especially since causality has yet to be established and understanding of mechanistic underpinnings is incomplete. Therefore, recommending their complete withdrawal, as the authors have also cautioned against, would certainly not be prudent as this patient population is largely immunocompromised and rather susceptible to infections. The cautious approach is one that is time tested- namely that abx should be used as a last resort and not as prophylaxis, especially when use of ICB agents is planned. If abx are required, then perhaps, treatment with a microbiome modulator following abx dosing to restore the eubiotic balance is warranted, though the jury is still out on whether such a reversal would indeed be possible [11]. Nevertheless, the case for judicious patient selection for treatment with abx, particularly broad-spectrum abx with anaerobic activity is certainly well made, and their potentially harmful impact on ICB response should not be completely overlooked.

References

[1] Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. Cancer Cell 2018;33:570–80.
[2] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science 2018;359:91–7.
[3] Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. Science 2018;359:104–8.
[4] Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103.
[5] Willing BP, Russell SL, Finlay BB. Shifting the balance: antibiotic effects on host-microbiota mutualism. Nat Rev Microbiol 2011;9:233–43.
[6] Huang X-Z, Gao P, Song Y-X, et al. Antibiotic use and the efficacy of immune checkpoint inhibitors in cancer patients: a pooled analysis of 2740 cancer patients. Oncoimmunology 2019;8:e1665973-e.
[7] Pinato DJ, Howlett S, Ottaviani D, et al. Association of Prior Antibiotic Treatment With Survival and Response to Immune Checkpoint Inhibitor Therapy in Patients With Cancer. JAMA Oncol 2019;5:1774–8.
[8] Yoon MY, Yoon SS. Disruption of the Gut Ecosystem by Antibiotics. Yonsei Med J 2018;59:4–12.
[9] Hopkins AM, Kichenadasse G, Karapetis CS, Rowland A, Sorich MJ. Concomitant antibiotic use and survival in urothelial carcinoma treated with atezolizumab. Eur Urol 2020;78:540–3.
[10] Kaderbhai C, Richard C, Fumet JD, et al. Antibiotic use does not appear to influence response to nivolumab. Anticancer Res 2017;37:3195–200.
[11] Pinato DJ, Gramenitskaya D, Altmann DM, et al. Antibiotic therapy and outcome from immune-checkpoint inhibitors. J Immunother Cancer 2019;7:287.

EUROPEAN UROLOGY 78 (2020) 546–569

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Urothelial Cancer

Editorial by Dominic C. Grimberg, Ankeet Shah and Brant A. Inman on pp. 570–571 of this issue

An International Collaborative Consensus Statement on En Bloc Resection of Bladder Tumour Incorporating Two Systematic Reviews, a Two-round Delphi Survey, and a Consensus Meeting

Jeremy Yuen-Chun Teoh [a,†], ***Steven MacLennan*** [b,†], ***Vinson Wai-Shun Chan*** [c], ***Jun Miki*** [d], ***Hsiang-Ying Lee*** [e], ***Edmund Chiong*** [f], ***Lui-Shiong Lee*** [g,h], ***Yong Wei*** [i], ***Yuhong Yuan*** [j], ***Chun-Pong Yu*** [k], ***Wing-Kie Chow*** [l], ***Darren Ming-Chun Poon*** [m], ***Ronald Chan*** [n], ***Fernand Lai*** [n], ***Chi-Fai Ng*** [a], ***Alberto Breda*** [o], ***Mario Wolfgang Kramer*** [p], ***Bernard Malavaud*** [q], ***Hugh Mostafid*** [r], ***Thomas Herrmann*** [s,t], ***Marek Babjuk*** [u,v,*]

[a] *S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China;* [b] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [c] *School of Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, UK;* [d] *Department of Urology, Jikei University School of Medicine, Kashiwa Hospital, Kashiwa, Japan;* [e] *Urology Department, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan;* [f] *Department of Urology, National University Hospital, National University Health System, Singapore;* [g] *Urology Service, Department of Surgery, Sengkang General Hospital, Sengkang, Singapore;* [h] *Department of Urology, Singapore General Hospital, Singapore;* [i] *Department of Urology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China;* [j] *Department of Medicine, McMaster University, Hamilton, Canada;* [k] *Li Ping Medical Library, The Chinese University of Hong Kong, Hong Kong, China;* [l] *New Territories East Cluster Bladder Cancer Support Group, Hong Kong, China;* [m] *Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China;* [n] *Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong, China;* [o] *Department of Urology, Fundacion Puigvert, Universitat Autonoma de Barcelona, Barcelona, Spain;* [p] *Department of Urology, University-Hospital Schleswig-Holstein, Campus Luebeck, Luebeck, Germany;* [q] *Department of Urology, Institut Universitaire du Cancer, Toulouse, France;* [r] *Department of Urology, Royal Surrey County Hospital, Guildford, Surrey, UK;* [s] *Department of Urology, Spital Thurgau AG, Frauenfeld, Switzerland;* [t] *Department of Urology, Hanover Medical School (MHH), Hanover, Germany;* [u] *Department of Urology, 2nd Faculty of Medicine, Hospital Motol, Charles University, Prague, Czech Republic;* [v] *Medical University of Vienna, Vienna, Austria*

Article info

Article history:
Accepted April 22, 2020

Associate Editor:
James Catto

Keywords:
Bladder cancer
En bloc resection of bladder tumour
Transurethral resection of bladder tumour
Urothelial carcinoma

Abstract

Background: There has been increasing interest in en bloc resection of bladder tumour (ERBT) as an oncologically noninferior alternative to transurethral resection of bladder tumour (TURBT) with fewer complications and better histology specimens. However, there is a lack of robust randomised controlled trial (RCT) data for making recommendations.
Objective: We aimed to develop a consensus statement to standardise various aspects of ERBT for clinical practice and to guide future research.
Design, setting, and participants: We developed the consensus statement on ERBT using a modified Delphi method. First, two systematic reviews were performed to investigate the clinical effectiveness of ERBT versus TURBT (effectiveness review) and to identify areas of uncertainty in ERBT (uncertainties review). Next, 200 health care professionals (urologists, oncologists, and pathologists) with experience in ERBT were invited to complete a two-round Delphi survey. Finally, a 16-member consensus panel meeting was held to review, discuss, and re-vote on the statements as appropriate.
Outcome measurements and statistical analysis: Meta-analyses were performed for RCT data in the effectiveness review. Consensus statements were developed from the

† Both authors contributed equally to this work.
* Corresponding author. Department of Urology, 2nd Faculty of Medicine, Hospital Motol, Charles University, Prague, Czech Republic. Tel.: +42 224 434 801; Fax: +42 224 967 102.
E-mail addresses: marek.babjuk@fnmotol.cz, babjuk@volny.cz (M. Babjuk).

https://doi.org/10.1016/j.eururo.2020.04.059

uncertainties review. Consensus was defined as follows: (1) ≥70% scoring a statement 7–9 and ≤15% scoring the statement 1–3 (consensus agree), or (2) ≥70% scoring a statement 1–3 and ≤15% scoring the statement 7–9 (consensus disagree).

Results and limitations: A total of 10 RCTs were identified upon systematic review. ERBT had a shorter irrigation time (mean difference −7.24 h, 95% confidence interval [CI] −9.29 to −5.20, $I^2 = 85\%$, $p < 0.001$) and a lower rate of bladder perforation (risk ratio 0.30, 95% CI 0.11–0.83, $I^2 = 1\%$, $p = 0.02$) than TURBT, both with moderate certainty of evidence. There were no significant differences in recurrences at 0–12, 13–24, or 25–36 mo (all very low certainty of evidence). A total of 103 statements were developed, of which 99 reached a consensus. A summary of statements is as follows: ERBT should always be considered for treating non–muscle-invasive bladder cancer; ERBT should be considered feasible even for bladder tumours larger than 3 cm; number and location of bladder tumours are not major limitations in performing ERBT; the planned circumferential margin should be at least 5 mm from any visible bladder tumour; after ERBT, additional biopsy of the tumour edge or tumour base should not be performed routinely; for the ERBT specimen, T1 substage, and circumferential and deep resection margins must be assessed; it is safe to give a single dose of immediate intravesical chemotherapy, perform second-look transurethral resection, and give intravesical bacillus Calmette-Guérin (BCG) therapy after ERBT; and in studies of ERBT, both per-patient and -tumour analysis should be performed for different outcomes as appropriate. Important outcomes for future ERBT studies were also identified. A limitation is that as consensus statements are brief, concise and binary in nature, areas of uncertainty that are complex in nature may not be addressed adequately.

Conclusions: We have provided the most comprehensive review of the evidence base to date using a meta-analysis where appropriate and applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and mobilised the international urology community to develop a consensus statement on ERBT using transparent and robust methods. The consensus statement will provide interim guidance for health care professionals who practice ERBT and inform researchers regarding ERBT-related studies in the future.

Patient summary: En bloc resection of bladder tumour (ERBT) is a surgical technique aiming to resect a bladder tumour in one piece. We included an international panel of experts to agree on the best practice of ERBT, and this will provide guidance to clinicians and researchers in the future.

1. Introduction

En bloc resection of bladder tumour (ERBT) was first described by Kitamura et al [1] in 1980. ERBT has three potential benefits in treating non–muscle-invasive bladder cancer (NMIBC) when compared with conventional transurethral resection of bladder tumour (TURBT). First, bladder tumour is resected in one piece and the tumour specimen remains intact for a proper histological assessment. Whether a complete resection has been achieved can be ascertained by histological means rather than the surgeon's judgement alone. Second, the resection process is more precise and controlled; thus, the complication profile, in particular the risk of bladder perforation, may be reduced. Third, ERBT can avoid tumour fragmentation as in the case of conventional piecemeal resection. It can potentially minimise the amount of floating tumour cells and reduce the risk of tumour reimplantation.

ERBT upholds the basic principles in cancer surgery, and it has gained increasing interests globally in the past decade. However, high-quality data are limited to make robust recommendations. There is a lack of standardisation leading to heterogeneity in the clinical and technical aspects of ERBT. It is important to develop a consensus statement on ERBT that can serve as a standard reference for health care professionals in the future. It will have important implications in our clinical practice as well as future studies of ERBT.

2. Patients and methods

We developed the consensus statement on ERBT using a modified Delphi method. The development process included two systematic reviews, a two-round Delphi survey, and a face-to-face consensus meeting (Fig. 1).

2.1. Systematic reviews

Two systematic reviews were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [2], and the study protocol was registered on PROSPERO [3]. The "effectiveness" review assessed the benefits and harms of ERBT compared with conventional TURBT and provided certainty of evidence ratings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [4,5]. The "uncertainties" review identified clinical and technical uncertainties in the area of ERBT. The findings of the systematic reviews provided the basis for the statements developed for voting in the Delphi survey and consensus meeting.

2.1.1. Search strategy

A comprehensive literature search to encompass the reviews of effectiveness and uncertainties was performed using a combination of

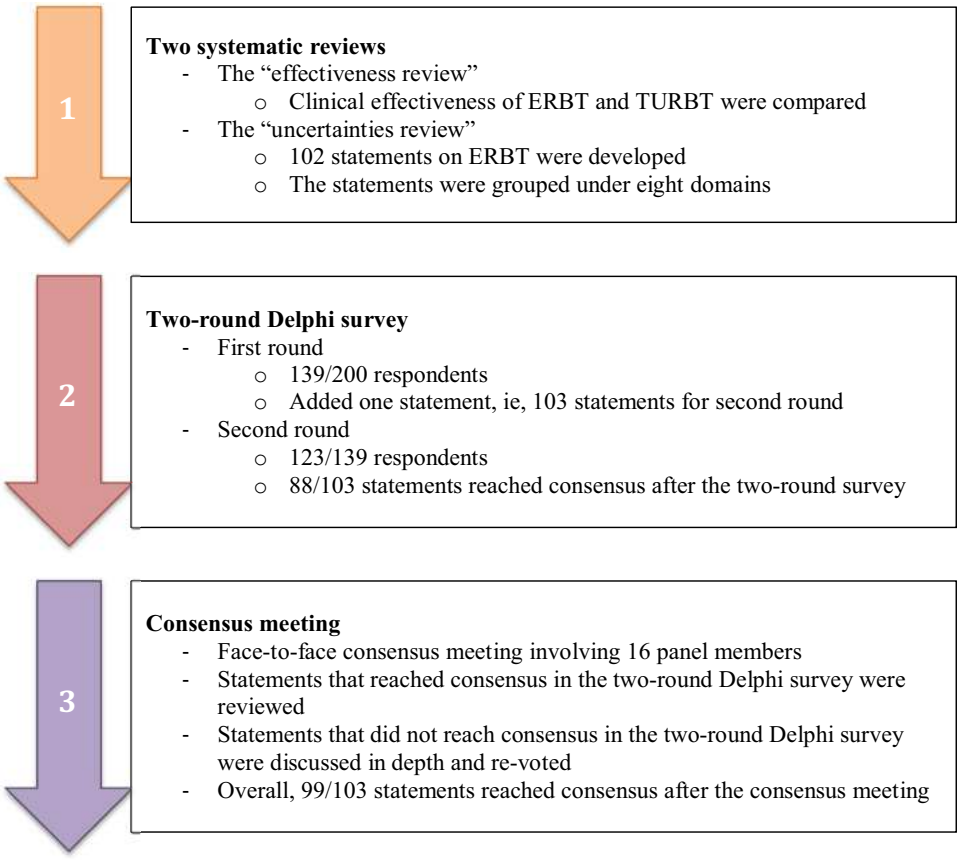


Fig. 1 – Overview of the development of the consensus statement.
ERBT = en bloc resection of bladder tumour; TURBT = transurethral resection of bladder tumour.

keywords (MeSH terms and free text words) related to "bladder tumour", and "'en bloc resection"/"ERBT". MEDLINE, EMBASE, and Cochrane library (CENTRAL and CDSR) were searched. The search strategy is presented in the Supplementary material. Additional references were sought from the reference lists of the included studies.

2.1.2. *Types of studies included*

All randomised and nonrandomised comparative studies, reported in journals or conference proceedings, were included in the effectiveness review. Single-arm case series or case reports were excluded from the effectiveness review but were retained for the uncertainties review. There was no cut-off date for the literature search. Only English-language articles were included. Conference proceedings, letters to editors, commentaries, and international guidelines were included in the uncertainties review.

2.1.3. *Assessment of risk of bias*

For the effectiveness review, the risk of bias in randomised controlled trials (RCTs) was assessed by using the recommended tool in the Cochrane Handbook for Systematic Reviews of Intervention [6]. The risk of bias in nonrandomised comparative studies was assessed with the same tool, with an extra item to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to assessing the risk of bias in nonrandomised studies, and it is the approach adopted in systematic reviews commissioned by the European Association of Urology (EAU) guidelines office to inform their guidelines [7].

2.1.4. *Data synthesis and statistical analysis*

For the effectiveness review, a meta-analysis was performed if there were two or more RCTs reporting on the same outcome. Data from RCT conference proceedings were included to reduce the risk of publication bias [6]. Reports of the same studies were linked together, where the reports containing the most complete data and longest follow-up were used. Relative risk (RR) and its 95% confidence interval (CI) were used to summarise statistic dichotomous data. Mean differences were used to summarise continuous data. Some clinical and methodological heterogeneity across the studies was suspected, and therefore a random effect model was used. Narrative synthesis, using the methods outlined in the Centre for Reviews and Dissemination handbook, were used to synthesise the results from nonrandomised studies [8]. Results from nonrandomised studies were not included in the quantitative analysis, as there may be significant selection bias, especially in the context of ERBT. Application of GRADE certainty of evidence was done in accordance with the GRADE handbook [9].

For the uncertainties review, areas of uncertainties in ERBT were extracted verbatim from any of the studies or sources meeting the inclusion criteria. The extracted data were categorised with reference to the usual management pathway and grouped under domains such as case selection, surgical procedure, postoperative management, and follow-up schedule. To reduce the data further, statements relating to the same concept were subsumed within one statement, resulting in a conceptual map of uncertainties identified in the ERBT literature. These statements were then used to create positively worded statements that can be agreed or disagreed with, for inclusion in the Delphi survey. The

statements were discussed within the steering group (J.Y.C.T., S.M., H.M., T.H., and M.B.) and finalised before proceeding to the Delphi survey.

2.2. Two-round Delphi survey

Delphi survey methods were used to promote anonymity and to control for the influence of dominant voices or perceived authoritative voices, yet still provided controlled feedback to participants [10].

2.2.1. Conduct of the two-round Delphi survey

The two-round Delphi survey was conducted using DelphiManager [11]. A total of 200 urologists, oncologists, and pathologists involved in the field of ERBT were purposively sampled for expertise and geographical location, to ensure that we covered an adequate breadth of international experience. The steering group provided the names of known experts in the field. This was supplemented by inviting the authors of studies included in the systematic reviews. Finally, in order to gather opinion from a more general perspective, a Twitter advert was promoted using the hashtags #ERBT and #UroSoMe [12]. Interested individuals were verified to have personal experience in ERBT before they were invited to participate in the online Delphi survey via an e-mail providing a link to the study. The link took them to a webpage providing information about the aims and objectives of the study, with a further link to a registration page. Informed consent was implied if the participant registered to take part.

As ERBT is heavily surgery oriented, a single heterogeneous panel model was used, as we did not think it is necessary to look for differences across stakeholder groups (ie, urologists, pathologists, and oncologists) [10,13]. Participants were asked to state their strength of agreement on a scale of 1 (strongly disagree) to 9 (strongly agree). There was also an "unable to score" option. Participants were instructed to choose "unable to score", rather than "5" (neither agree nor disagree) if they felt they did not have enough knowledge or expertise on a particular statement, because these two concepts are qualitatively different. We made this explicit because this phenomenon has been noted as a limitation in other consensus projects [14,15]. During the first round, participants could suggest additional items to be incorporated into the second round of survey (subjected to review by the steering group). Only those who had completed the first-round survey could participate in the second-round survey. In the second round, they were reminded of their own round 1 score and were shown a distribution of the group scores across the 1–9 scale for each statement. They were allowed to use this information to consider retaining their previous scores or changing their scores relative to the field. All voting results were anonymous to minimise bias and influence regarding agreeing with dominant or authoritative voices.

2.2.2. Definition of consensus and analysis plan

Consensus is defined as follows: (1) $\geq$70% scoring a statement 7–9 and $\leq$15% scoring the statement 1–3 (consensus agree), or (2) $\geq$70% scoring a statement 1–3 and $\leq$15% scoring the statement 7–9 (consensus disagree). This definition has been used in other urology consensus meetings [14–16] and achieves a balance between being overinclusive and -exclusive whilst still allowing a consideration of variance (ie, spread or divergent opinions) [17].

2.3. Consensus meeting

A consensus meeting was held to review the statements that reached consensus in the Delphi survey, and to discuss in-depth and re-vote on those statements upon which there was no consensus. The consensus panel consisted of 16 members, including 12 urologists, one oncologist, one pathologist, one methodologist (nonvoting member), and one patient representative. The meeting was chaired by the methodologist with experience in chairing consensus meetings and no conflicts of interest regarding ERBT. First, the results of the effectiveness review were presented and discussed. Next, the two-round Delphi survey results were discussed. Panel members were provided with a hard-copy overview of the Delphi voting results for both rounds, along with a reminder of their own votes in both rounds. Statements where there was a clear consensus were reviewed to ensure that the results were sensible. Then statements in which more than five participants had chosen "unable to score" were reviewed to explore reasons for this. Finally, statements not reaching a consensus in the Delphi survey were discussed in depth before anonymous voting using their own smart devices and the Poll Everywhere software [18]. The same consensus definitions were used.

3. Results

3.1. Systematic review and meta-analysis

The PRISMA flow diagram is shown in Figure 2. The initial search yielded 669 records. After removing duplicates, 430 articles were screened based on title and abstract. For the effectiveness review, 44 articles were reviewed in full text. At the end of the process, 32 studies (with 39 reports) were included in qualitative synthesis. Among them, 10 were RCTs (with 13 reports) [19–31], and these were included in a quantitative analysis. For the uncertainties review, 151 articles were reviewed in full text and included for generation of consensus statements. The studies included in the uncertainties review are listed in the Supplementary material.

Table 1 summarises the study characteristics of the RCTs. Only data from RCTs were extracted for subsequent meta-analysis. Risk of bias assessment of the RCTs is presented in Figure 3. Study characteristics and risk of bias assessment of the nonrandomised studies and the GRADE summary of finding profiles are included in the Supplementary material.

3.1.1. Effectiveness review—outcome measures from RCTs

ERBT had a longer operative time than TURBT (mean difference 9.07 min, 95% CI 3.36–14.79, $I^2 = 86\%$, $p = 0.002$; very low certainty evidence). ERBT had a shorter irrigation time than TURBT (mean difference −7.24 h, 95% CI −9.29 to −5.20, $I^2 = 85\%$, $p < 0.001$; moderate certainty evidence), but there were no significant differences in the catheterisation time (mean difference −0.90 d, 95% CI −2.21 to 0.41, $I^2 = 97\%$, $p = 0.18$; low certainty evidence) and hospital stay (mean difference −1.32 d, 95% CI −2.71 to 0.06, $I^2 = 97\%$, $p = 0.06$; low certainty evidence). Although there was no significant difference in the occurrence of obturator nerve reflex (RR 0.19, 95% CI 0.03–1.22, $I^2 = 79\%$, $p = 0.08$; very low certainty evidence), ERBT had a lower rate of bladder perforation than TURBT (RR 0.30, 95% CI 0.11–0.83, $I^2 = 1\%$, $p = 0.02$; moderate certainty evidence). Presence of detrusor muscle in specimen was similar between ERBT and TURBT (RR 1.11, 95% CI 0.40–3.11, $I^2 = 77\%$, $p = 0.84$; very low certainty evidence). There were no significant differences in 0–12 mo (RR 0.82, 95% CI 0.56–1.19, $I^2 = 12\%$, $p = 0.29$), 13–24 mo (RR 0.79, 95% CI 0.44–1.42, $I^2 = 0\%$, $p = 0.43$), and 25–36 mo (RR 0.89, 95% CI 0.65–1.22, $I^2 = 47\%$, $p = 0.47$) recurrence rates (all very low certainty evidence). Data were too limited for the subgroup

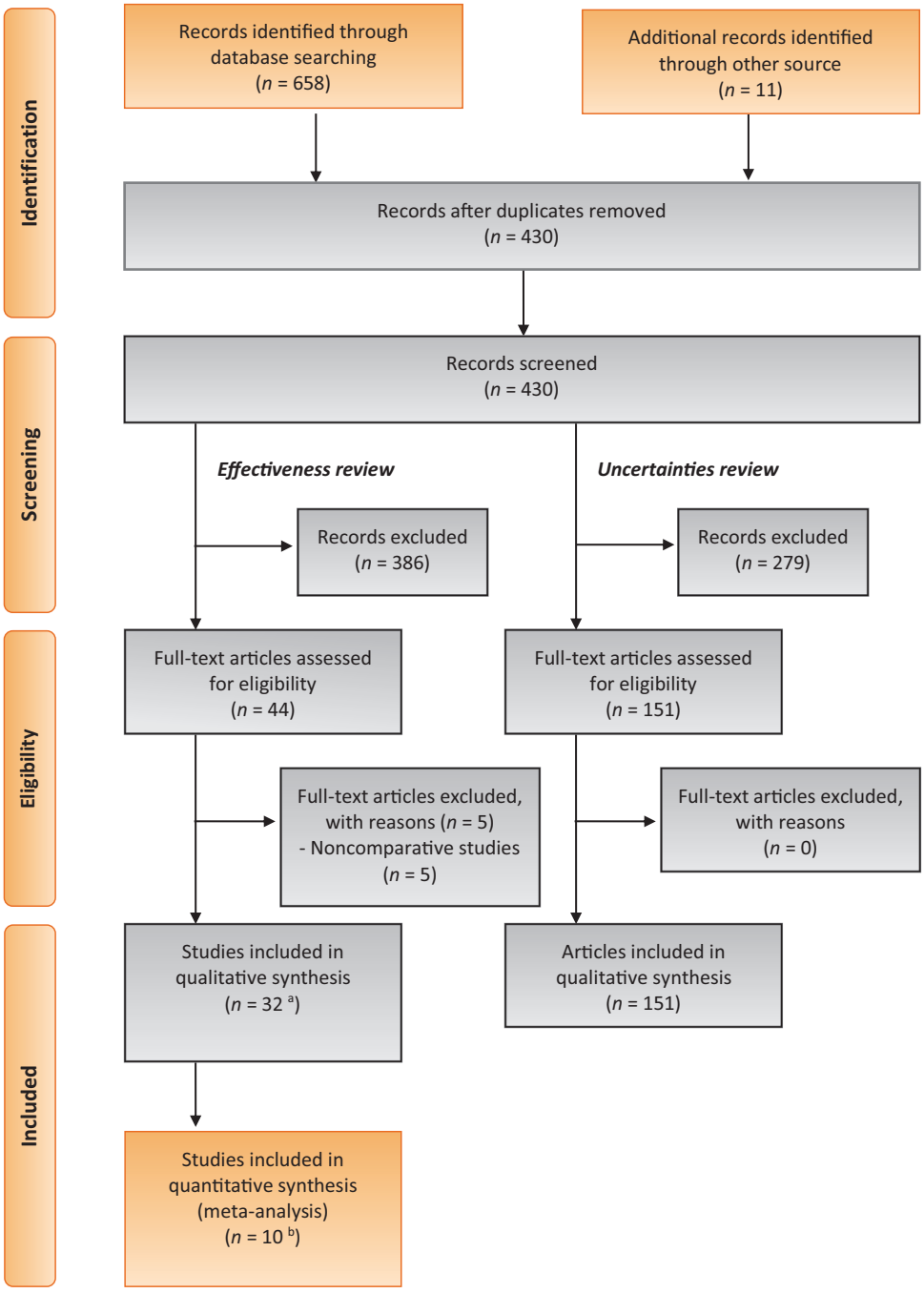


Fig. 2 – PRISMA flow diagram.
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.
[a]Thirty-two studies with 39 reports.
[b]Ten studies with 13 reports.

comparisons between different modalities of ERBT and TURBT. The key findings of the meta-analysis are summarised in Figure 4, and other results are summarised in the Supplementary material.

3.1.2. Effectiveness review—outcome measures from nonrandomised studies

Most studies showed that ERBT had a shorter irrigation time and a lower rate of bladder perforation than TURBT, and this is in line with the RCT data. However, the results on the operative time were controversial. Most studies showed that ERBT had a shorter catheterisation time, shorter hospital stay, lower rate of obturator nerve reflex, and higher rate of detrusor muscle than TURBT. Most studies also showed lower 0–12, 13–24, and 25–36 mo recurrence rates in favour of ERBT. All outcomes were judged to be at low or very low certainty of evidence. The results are summarised in the Supplementary material.

3.2. Uncertainties review—generation of consensus statements

Based on the results of the systematic review, 102 statements were generated for the first-round survey. After the first-round survey, one additional statement was added, resulting in 103 statements in total for the second-round survey.

The statements were grouped under eight domains as follows.

1 Definitions and objectives of ERBT.
2 Case selection.
3 Surgical procedure.
4 Different modalities of ERBT.
5 Reporting of intraoperative findings.
6 Specimen preparation and reporting of histological findings.
7 Postoperative management and follow-up schedule.
8 Data reporting and outcome measures.

3.3. Two-round Delphi survey

In the first-round survey, there were 139 respondents out of 200 invitations (69.5%). Among the first-round survey respondents, 123 completed the second-round survey (88.5%). There was a wide coverage of respondents globally, with the majority practising in Europe and Asia. The majority had >10 yr of clinical practice; 90.2% were urologists, 6.5% were pathologists, and 3.3% were oncologists. This is reflective of the situation that NMIBC is

Table 1 – Study characteristics of included randomised controlled trials.

Study	Country	Eligibility criteria	Comparison	Total (*n*)	ERBT arm (*n*)	Control arm (*n*)
Balan et al (2018) [19], Geavlete et al (2018) [20], and Geavlete et al (2019) [21] [a]	Romania	NMIBC 1–3 cm in diameter No solid sessile tumours Not located at bladder neck or involving the ureteral orifice	Bipolar ERBT vs monopolar TURBT	90	45	45
Chen et al (2015) [22]	China	Primary NMIBC No suspicion of MIBC No serious heart, lung, or brain conditions	Thulium laser ERBT vs TURBT[b]	142	71	71
Cheng et al (2016) [23]	China	NMIBC	HybridKnife ERBT vs TURBT[b]	75	38	37
Gakis et al (2017) [24]	Germany	NMIBC Tumour size >5 mm	HybridKnife ERBT vs TURBT[b]	115	56	59
Hu et al (2017) [25] and Hu et al (2018) [26][a]	China	Primary NMIBC Not CIS Not >3 cm and not <1 cm in diameter Not more than 5 tumours	HybridKnife ERBT vs TURBT[b]	93	46	47
Kufner et al (2014) [27]	Germany	Superficial papillary bladder tumour	HybridKnife ERBT vs TURBT[b]	16	7	9
Li et al (2014) [28]	China	NMIBC	ERBT[b] vs TURBT[b]	158	80	78
Liu et al (2013) [29]	China	Newly diagnosed NMIBC Not urothelial papillomas Not MIBC or CIS No upper urinary tract tumours No extravesical extension, lymphatic metastasis, or invasion of adjacent organs	Thulium laser ERBT vs monopolar TURBT	120	64	56
Ruffo et al (2017) [30]	Italy	Newly diagnosed NMIBC	Thulium laser ERBT vs monopolar TURBT	54	30	24
Zhang et al (2015) [31]	China	Primary NMIBC Not inverted papilloma No extravesical extension, lymph node metastasis, or adjacent organ invasion No upper urinary tract tumours Excluded patients who could not tolerate general anaesthesia No severe cardiovascular or pulmonary disease, or disturbance of blood coagulation contradicting operation	Thulium laser ERBT vs bipolar TURBT	292	149	143

CIS = **c**arcinoma in situ; ERBT = **e**n bloc resection of bladder tumour; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; TURBT = **t**ransurethral resection of bladder tumour.
[a] Same study with numerous reports; report with the most complete data and longest follow-up was presented.
[b] Unknown energy source.

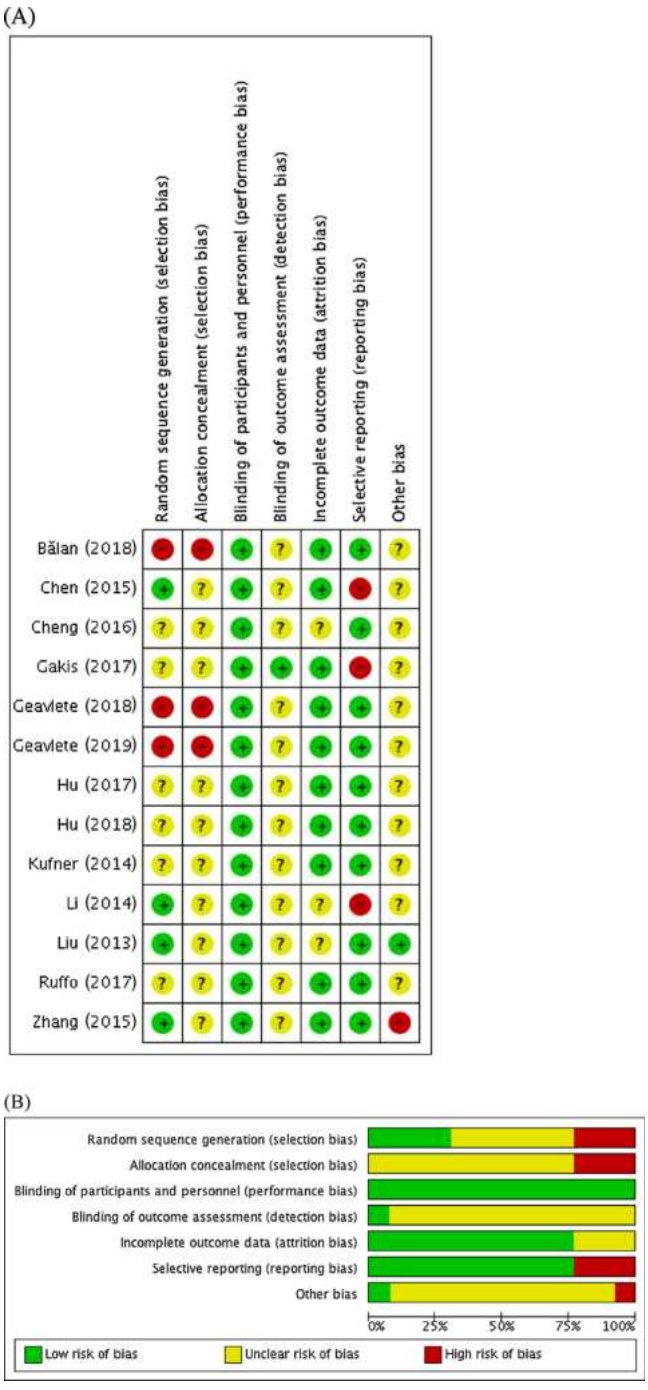


Fig. 3 – Risk of bias assessment of the randomised controlled trials.

managed mostly by urological surgeons. Table 2 summarises the characteristics of the Delphi participants completing both rounds of survey. After the two-round Delphi survey, a consensus was reached in 88 out of 103 statements (85.4%).

3.4. Consensus panel meeting

Table 3 lists the characteristics of the panel members. After the discussion and re-voting processes, the consensus panel

Table 2 – Characteristics of the Delphi participants who completed both rounds of survey.

		Round 1 *N* (%)	Round 2 *N* (%)
Region			
	Africa	4 (2.9)	2 (1.6)
	Asia	70 (50.4)	62 (50.4)
	Australia/New Zealand	2 (1.4)	2 (1.6)
	Europe	53 (38.1)	48 (39.0)
	North America	3 (2.2)	2 (1.6)
	South America	7 (5.0)	7 (5.7)
Years of practice			
	1–5	15 (10.8)	14 (11.4)
	6–10	37 (26.6)	33 (26.8)
	11–15	41 (29.5)	36 (29.3)
	16–20	26 (18.7)	23 (18.7)
	21–25	12 (8.6)	9 (7.3)
	26–30	5 (3.6)	5 (4.1)
	>30	3 (2.2)	3 (2.4)
Speciality			
	Oncologist	6 (4.3)	4 (3.3)
	Pathologist	8 (5.8)	8 (6.5)
	Urologist	125 (89.9)	111 (90.2)
Total		139 (100)	123 (100)

was able to reach a consensus in 11 out of 15 statements. Overall, 99 out of 103 statements (96.1%) reached a consensus after the whole development process.

3.5. Principal findings of the consensus statement

Table 4 summarises the results of all statements and consensus status after two rounds of survey. Table 5 summarises the statements that were discussed and re-voted, and their consensus status after the voting session. The final results of the consensus statements on ERBT are summarised in Table 6.

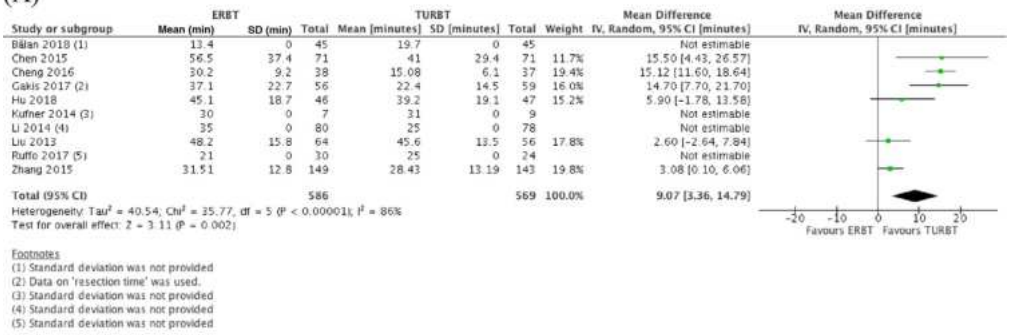
3.5.1. Definitions and objectives of ERBT

Removal of bladder tumour in one piece [32] is the most appropriate definition for ERBT. The main goals of ERBT are to ensure complete local resection of bladder tumour, ensure proper local staging of the disease, and reduce the risk of tumour reimplantation. Upon ERBT, we must aim to include the detrusor muscle layer in the specimen. ERBT should always be considered for treating NMIBC [19,22–26,28–30]. However, in cases of muscle-invasive bladder cancer (MIBC) and carcinoma in situ (CIS) of the bladder, ERBT should not be considered [22,25,26,29].

3.5.2. Case selection

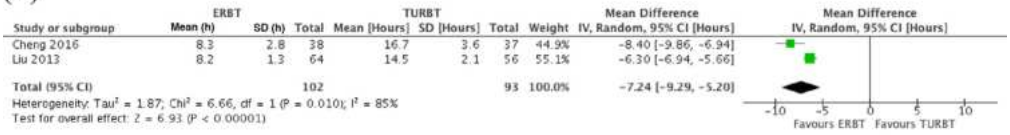
3.5.2.1. Size of bladder tumour. Size of bladder tumour is a major limitation in performing ERBT. Most studies used bladder tumour size of 3 cm as a cut-off in performing ERBT [19,25,26,33,34]. In the Delphi survey, it was agreed that ERBT is feasible for bladder tumour size of $\leq$3 cm. For bladder tumour size of >3 cm, no consensus was reached in the Delphi survey. The panel members agreed that, in such situation, it might be difficult to extract the specimen in one piece. However, the resection procedure itself is still

(A)

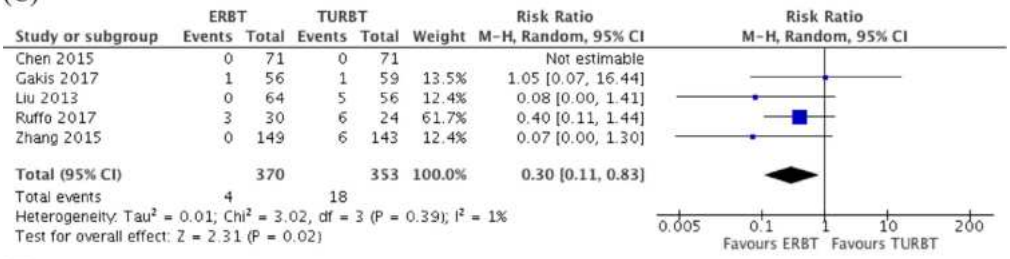


Footnotes
(1) Standard deviation was not provided
(2) Data on 'resection time' was used.
(3) Standard deviation was not provided
(4) Standard deviation was not provided
(5) Standard deviation was not provided

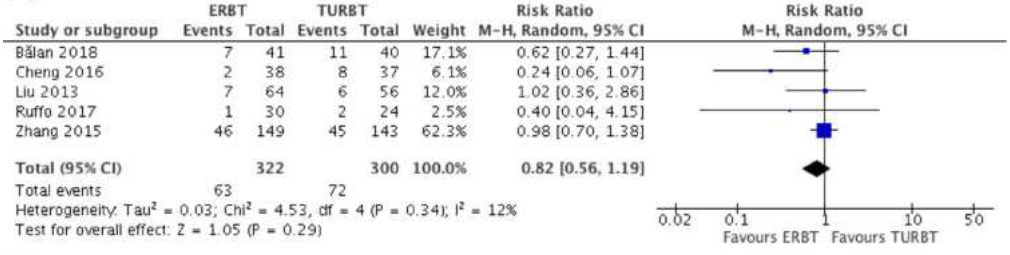
(B)



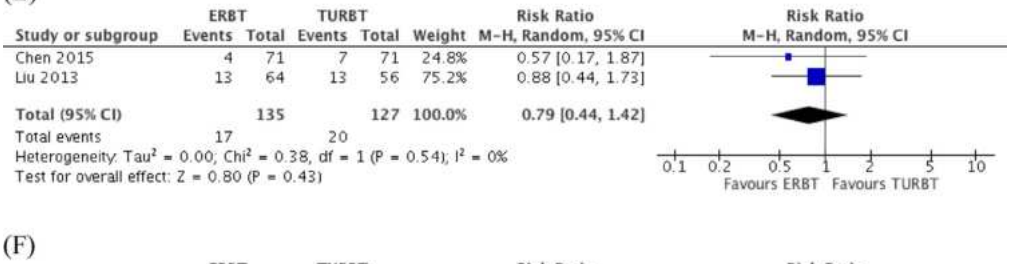
(C)



(D)



(E)



(F)

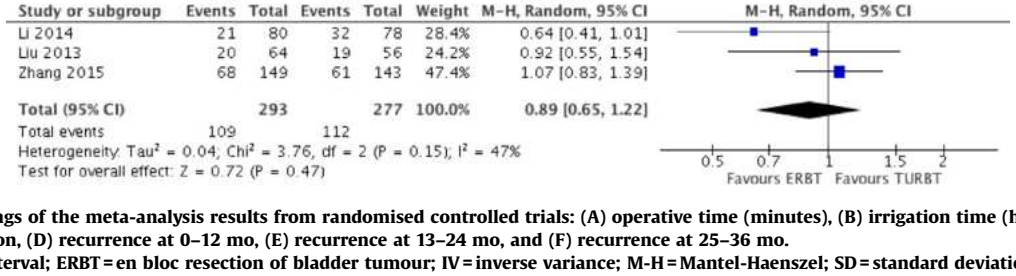


Fig. 4 – Key findings of the meta-analysis results from randomised controlled trials: (A) operative time (minutes), (B) irrigation time (hours), (C) bladder perforation, (D) recurrence at 0–12 mo, (E) recurrence at 13–24 mo, and (F) recurrence at 25–36 mo.
CI = confidence interval; ERBT = en bloc resection of bladder tumour; IV = inverse variance; M-H = Mantel-Haenszel; SD = standard deviation; TURBT = transurethral resection of bladder tumour.

Table 3 – Panel members of the consensus meeting.

Name	Role	Representing body/institution
Steven MacLennan	Chair (methodologist)	University of Aberdeen, UK
Darren Poon	Oncologist	The Chinese University of Hong Kong, Hong Kong, China
Fernand Lai	Pathologist	The Chinese University of Hong Kong, Hong Kong, China
Chow Wing-Kie	Patient	New Territories East Cluster Bladder Cancer Support Group, Hong Kong, China
Alberto Breda	Urologist	Fundacion Puigvert, Universitat Autonoma de Barcelona, Spain
Bernard Malavaud	Urologist	Institut Universitaire du Cancer, France
Edmund Chiong	Urologist	National University Hospital, National University Health System, Singapore
Hugh Mostafid	Urologist	Royal Surrey County Hospital, UK
Jeremy Teoh	Urologist	The Chinese University of Hong Kong, Hong Kong, China
Jun Miki	Urologist	Jikei University School of Medicine, Japan
Lee Hsiang-Ying	Urologist	Kaohsiung Municipal Ta-Tung Hospital, Taiwan
Lee Lui-Shiong	Urologist	Sengkang General Hospital, Singapore General Hospital, Singapore
Marek Babjuk	Urologist	Hospital Motol, Charles University, Czech Republic; Medical University of Vienna, Austria
Mario Kramer	Urologist	University Clinic of Schleswig-Holstein, Campus Luebeck, Germany
Thomas Herrmann	Urologist	Spital Thurgau AG, Switzerland; Hanover Medical School (MHH), Germany
Wei Yong	Urologist	First Affiliated Hospital of Fujian Medical University, China

technically possible [22,29,35–38], and the potential benefits of ensuring proper staging and complete resection of NMIBC can still be preserved. Therefore, the panel members concluded that ERBT should be regarded as a feasible surgical approach even for bladder tumours larger than 3 cm.

3.5.2.2. Number of bladder tumours. The number of bladder tumours is not a major limitation in performing ERBT. Most studies used four bladder tumours as a cut-off in performing ERBT [39–43]. In the Delphi survey, it was agreed that ERBT is feasible for patients with fewer than four bladder tumours. For patients with more than four bladder tumours, no consensus was reached in the Delphi survey. The panel members agreed that, in such situation, it might take more time and effort to perform ERBT. However, ERBT is still feasible in most of the patients within a reasonable operative time [29,33]. Therefore, the panel members concluded that ERBT should be regarded as a feasible surgical approach even for patients with more than four bladder tumours.

3.5.2.3. Tumour location. Tumour location is not a major limitation in performing ERBT. In the Delphi survey, it was agreed that ERBT is feasible for bladder tumours located at the posterior wall, anterior wall, right lateral wall, left lateral wall, trigone, bladder neck, and near the ureteric orifice areas. Although no consensus was reached for bladder tumours located at the bladder dome in the Delphi survey, there was a 100% consensus in the panel meeting that ERBT is feasible in such tumour location. The panel members concluded that, although bladder dome tumours might be more technically difficult to resect, by allowing more time for resection and with relevant experience [38,44], ERBT is still a feasible approach in such situations.

3.5.3. Surgical procedure

As bladder cancer changes can be subtle, a thorough cystoscopic examination must be performed before any ERBT [22,34,36,45]. However, the evidence on the use of enhanced imaging (narrow-band imaging, Image 1S, or photodynamic diagnosis) is limited, especially in the context of ERBT, and no consensus was reached in this aspect. The bladder should be distended enough, but not overdistended [29,37], to facilitate ERBT while avoiding bladder perforation during the procedure. The planned circumferential margin should be marked first to facilitate subsequent ERBT [35,37,44,45], and it should be at least 5 mm from any visible bladder tumour [34,36,37]. The depth of incision should be made at the detrusor muscle layer [19,22,34,36,37,44,45]. As ERBT specimens can provide comprehensive information regarding the depth of tumour invasion and resection margins [33,35,46–48], additional biopsy of the tumour base and tumour edge should not be performed routinely after ERBT. If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered. If the bladder tumour is too large, after ERBT, dividing the specimen into two to three pieces for retrieval [45,49] can be considered. If any technical difficulty is encountered upon ERBT, conversion to conventional TURBT should be considered. Special extraction methods can be considered in retrieving large ERBT specimens [35,49,50].

3.5.4. Different modalities of ERBT

It is technically feasible to use monopolar energy [37,48,49], bipolar energy [19–21,46–48,51], holmium laser [33,48,52], thulium laser [22,29,30,48], and HybridKnife (hydrodissection) [24–27,35] to perform ERBT. Monopolar and bipolar ERBT techniques allow conversion to piecemeal resection readily when technical difficulty arises. Holmium and thulium laser ERBT techniques eliminate the risk of obturator nerve reflex during the procedure [22,29,33,44]. There is however a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation [35,53].

3.5.5. Reporting of intraoperative findings

The EAU guidelines stated that the operative record of conventional TURBT must describe tumour location, ap-

Table 4 – Summary of statements and consensus status after two rounds of Delphi survey.

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
Definitions and objectives of ERBT													
1	Removal of bladder tumour in one piece is the most appropriate definition for ERBT	3.6	9.4	87.0	139	1	Agree	0.8	6.5	92.7	123	0	Agree
2	The depth of ERBT must include the detrusor muscle layer in the specimen	5.8	9.4	84.8	139	1	Agree	4.1	7.3	88.6	123	0	Agree
3	One of the main goals of ERBT is to ensure complete local resection of bladder tumour	0.7	3.6	95.7	139	1	Agree	0.8	0.8	98.4	123	0	Agree
4	One of the main goals of ERBT is to ensure proper local staging of the disease	0.7	0	99.3	139	2	Agree	1.6	0	98.4	123	1	Agree
5	One of the main goals of ERBT is to reduce the risk of tumour reimplantation	8.8	14.6	76.6	139	2	Agree	4.1	15.7	80.2	123	2	Agree
6	ERBT should always be considered for treatment of non–muscle-invasive bladder cancer	8.8	24.8	66.4	139	2	Not reached	4.9	17.2	77.9	123	1	Agree
7	ERBT should be considered for treatment of muscle-invasive bladder cancer	53.7	26.5	19.9	139	3	Not reached	63.9	19.7	16.4	123	1	Not reached
8	ERBT should be considered to treat carcinoma in situ of the bladder to optimise subsequent treatment	48.1	31.1	20.7	139	4	Not reached	56.3	26.1	17.6	123	4	Not reached
Case selection													
9	Size of bladder tumour is a major limitation in performing ERBT	8.8	6.6	84.6	139	3	Agree	9.2	3.3	87.5	122	2	Agree
10	ERBT is feasible for patients with bladder tumour size of <3 cm	2.2	4.4	93.3	139	4	Agree	1.7	1.7	96.6	122	3	Agree
11	ERBT is feasible for patients with bladder tumour size of more than 3cm	21.1	41.4	37.6	139	6	Not reached	15.3	37.3	47.5	122	4	Not reached
12	Number of bladder tumours is a major limitation in performing ERBT	36.5	29.9	33.6	139	2	Not reached	38.3	17.5	44.2	122	2	Not reached
13	If tumour size is not an issue, ERBT is feasible for patients with <4 bladder tumours	7.4	13.3	79.3	139	4	Agree	5.0	5.0	89.9	122	3	Agree
14	If tumour size is not an issue, ERBT is feasible for patients with >4 bladder tumours	18.8	34.6	46.6	139	6	Not reached	15.1	21.8	63.0	122	3	Not reached
15	Tumour location is a major limitation in performing ERBT	20.9	23.1	56.0	139	5	Not reached	16.1[b]	12.7	71.2	122	4	Not reached
16	ERBT is feasible for bladder tumour located at the posterior wall	3.0	5.9	91.1	139	4	Agree	1.7	0.8	97.5	122	4	Agree
17	ERBT is feasible for bladder tumour located at the anterior wall	14.9	26.9	58.2	139	5	Not reached	12.8	14.5	72.6	122	5	Agree
18	ERBT is feasible for bladder tumour located at the right lateral wall	0.7	5.9	93.3	139	4	Agree	0	3.4	96.6	122	4	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
19	ERBT is feasible for bladder tumour located at the left lateral wall	1.5	5.9	92.6	139	4	Agree	0	3.4	96.6	122	4	Agree
20	ERBT is feasible for bladder tumour located at the trigone	2.2	8.1	89.6	139	4	Agree	0.8	2.5	96.6	122	4	Agree
21	ERBT is feasible for bladder tumour located at the bladder dome	17.8	30.4	51.9	139	4	Not reached	16.9	22.0	61.0	122	4	Not reached
22	ERBT is feasible for bladder tumour located at the bladder neck	13.4	15.7	70.9	139	5	Agree	10.3	7.7	82.1	122	5	Agree
23	ERBT is feasible for bladder tumour located near the ureteric orifice	11.2	17.2	71.6	139	5	Agree	7.6	9.3	83.1	122	4	Agree
Surgical procedure													
24	A thorough cystoscopic examination must be performed before any ERBT	3.0	3.8	93.2	137	4	Agree	0.8	0	99.2	122	3	Agree
25	Narrow-band imaging, Image 1S, or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	19.5	30.9	49.6	137	14	Not reached	14.4	26.1	59.5	122	11	Not reached
26	The bladder should be distended enough to facilitate ERBT	12.7	22.4	64.9	137	3	Not reached	9.2	11.8	79.0	122	3	Agree
27	The bladder should not be overdistended to avoid bladder perforation upon ERBT	4.6	10.7	84.7	137	6	Agree	4.3	5.1	90.6	122	5	Agree
28	The planned circumferential margin should be marked first to facilitate subsequent ERBT	4.5	14.4	81.1	137	5	Agree	1.7	6.8	91.5	122	4	Agree
29	Upon ERBT, the planned circumferential margin should be at least 5 mm from any visible bladder tumour	7.6	18.2	74.2	137	5	Agree	3.4	11.0	85.6	122	4	Agree
30	Upon ERBT, the incision should be made deep into the detrusor muscle layer	12.9	12.1	75.0	137	5	Agree	11.1	6.8	82.1	122	5	Agree
31	After ERBT, additional biopsy of the tumour base should be performed routinely	39.8	24.1	36.1	137	4	Not reached	45.8	17.8	36.4	122	4	Not reached
32	After ERBT, additional biopsy of the tumour edge should be performed routinely	47.3	27.5%	25.2%	137	6	Not reached	62.4%	21.4%	16.2	122	5	Not reached
33	If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered	3.0	8.3	88.6	137	5	Agree	1.7	3.4	94.9	122	4	Agree
34	If the size of bladder tumour is too big, after ERBT, dividing the specimen into 2–3 pieces for retrieval can be considered	12.2	22.1	65.6	137	6	Not reached	8.5	12.8	78.6	122	5	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
35	If any technical difficulty is encountered upon ERBT, conversion to conventional TURBT should be considered	1.5	3.0	95.5	137	3	Agree	0.8	0.8	98.3	122	3	Agree
36	Special extraction methods (Endobag, laparoscopic instrument through nephroscope, etc.) can be considered in retrieving large ERBT specimens	12.2	11.4	76.4	137	14	Agree	8.1	7.2	84.7	122	11	Agree
Different modalities of ERBT													
37	It is technically feasible to use monopolar energy for ERBT	7.5	20.8	71.7	135	15	Agree	5.5	11.0	83.5	122	13	Agree
38	It is technically feasible to use bipolar energy for ERBT	0.8	3.2	96.0	135	10	Agree	0	0.9	99.1	122	9	Agree
39	It is technically feasible to use holmium laser for ERBT	1.8	19.6	78.6	135	23	Agree	2.0	12.9	85.1	122	21	Agree
40	It is technically feasible to use thulium laser for ERBT	2.1	20.0	77.9	135	40	Agree	1.1	11.1	87.8	122	32	Agree
41	It is technically feasible to use HybridKnife (hydrodissection) for ERBT	3.4	26.1	70.5	135	47	Agree	0	18.1	81.9	122	39	Agree
42	ERBT using monopolar energy allows conversion to piecemeal resection readily when technical difficulty arises	6.7	12.6	80.7	135	16	Agree	4.5	6.4	89.1	122	12	Agree
43	ERBT using bipolar energy allows conversion to piecemeal resection readily when technical difficulty arises	0.8	9.0	90.2	135	13	Agree	0	5.3	94.7	122	9	Agree
44	Holmium laser eliminates the risk of obturator nerve reflex during ERBT	1.0	20.4	78.6	135	32	Agree	0	8.1	91.9	122	23	Agree
45	Thulium laser eliminates the risk of obturator nerve reflex during ERBT	1.1	24.7	74.2	135	42	Agree	0	8.9	91.1	122	32	Agree
46	HybridKnife (hydrodissection) is the safest modality for performing ERBT	18.1	50.6%	31.3%	135	52	Not reached	18.2	57.1	24.7	122	45	Not reached
47	There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	11.3	47.5	41.3	135	55	Not reached	7.7	52.6	39.7	122	44	Not reached
Reporting of intraoperative findings for patients undergoing ERBT													
48	The modality used for ERBT must be documented	0	3.0	97.0	135	1	Agree	0	0.8	99.2	122	1	Agree
49	Whether ERBT has been successfully performed or any need of conversion to conventional TURBT must be documented	0	1.5	98.5	135	1	Agree	0	0.8	99.2	122	1	Agree
50	Whether additional biopsy of the tumour base has been performed must be documented	0	3.7	96.3	135	1	Agree	0	0.8	99.2	122	1	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
51	Whether additional biopsy of the tumour edge has been performed must be documented	2.2	4.5	93.3	135	1	Agree	0.8	0.8	98.3	122	1	Agree
52	The EAU guidelines stated that the operative record of TURBT must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection	0	0	100.0	135	1	Agree	0	0	100.0	122	1	Agree
53	Any occurrence of obturator nerve reflex and the laterality of obturator nerve reflex being encountered during ERBT must be documented	2.3	18.8	78.9	135	2	Agree	0	9.9	90.1	122	1	Agree
54	Any occurrence of extra- or intraperitoneal bladder perforation during ERBT must be documented	0.7	1.5	97.8	135	1	Agree	0.8	0	99.2	122	1	Agree
55	The method of tumour extraction must be documented	1.5	4.5	94.0	135	1	Agree	0	0	100.0	122	1	Agree
56	Any difficulty in tumour extraction must be documented	1.5	6.7	91.8	135	1	Agree	0	4.1	95.9	122	1	Agree
57	Whether the ERBT specimen has been divided for extraction must be documented	0.7	5.2	94.0	135	1	Agree	0	0.8	99.2	122	1	Agree
Specimen preparation and reporting of histological findings													
58	Every ERBT specimen must be prepared and sent for histological assessment separately	1.5	6.0	92.5	135	2	Agree	0.8	3.3	95.8	121	1	Agree
59	For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	7.9	31.0	61.1	135	9	Not reached	5.2	30.4	64.3	121	6	Not reached
60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	14.3	32.5	53.2	135	9	Not reached	8.0	31.0	61.1	121	8	Not reached
61	For the ERBT specimen, it should be serially sectioned at 2 mm intervals	3.1	38.1	58.8	135	38	Not reached	0	29.2	70.8	121	32	Agree
62	The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, and presence of carcinoma in situ and detrusor muscle	0	3.0	97.0	135	1	Agree	0	2.5	97.5	121	1	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
63	Upon histological assessment of the ERBT specimen, the maximal dimension of bladder tumour must be documented	5.8	22.3	71.9	135	14	Agree	2.7	12.7	84.5	121	11	Agree
64	Upon histological assessment of the ERBT specimen, T1 substage must be assessed	1.5	10.4	88.1	135	1	Agree	0.8	8.3	90.8	121	1	Agree
65	Upon histological assessment of the ERBT specimen, circumferential resection margin must be assessed	3.0	6.7	90.3	135	1	Agree	4.2	2.5	93.3	121	1	Agree
66	Upon histological assessment of the ERBT specimen, deep resection margin must be assessed	0.7	3.0	96.3	135	1	Agree	0	1.7	98.3	121	1	Agree
Postoperative management and follow-up schedule													
67	It is safe to give a single dose of intravesical chemotherapy immediately after ERBT	4.7	14.2	81.1	135	8	Agree	1.7	6.1	92.2	121	6	Agree
68	The indications of a single dose of intravesical chemotherapy immediately after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	2.3	9.9	87.8	135	4	Agree	1.7	4.3	94.0	121	4	Agree
69	It is safe to perform second-look TURBT after the first ERBT	3.9	11.6	84.5	135	6	Agree	2.5	6.8	90.7	121	3	Agree
70	Indications of second-look TURBT after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	10.0	14.6	75.4	135	5	Agree	7.0	10.4	82.6	121	6	Agree
71	It is safe to give intravesical BCG therapy after ERBT	3.9	7.0	89.1	135	6	Agree	1.7	5.1	93.2	121	4	Agree
72	Indications of intravesical BCG therapy after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	1.5	3.8	94.7	135	4	Agree	0	3.4	96.6	121	3	Agree
73	The flexible cystoscopy surveillance protocol after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	0	4.5	95.5	135	2	Agree	0	3.4	96.6	121	2	Agree
74 [c]	Upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in-field and out-of-field recurrence	–	–	–	–	–	–	0.9	2.6	96.5	121	7	Agree
Data reporting and outcome measures													
75	In studies of ERBT, both per-patient and per-tumour analyses should be performed for different outcomes	3.8	10.6	85.6	135	3	Agree	1.7	5.0	93.3	121	1	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
76	In studies of ERBT, the operative time is an important outcome to measure	10.7	26.0	63.4	135	4	Not reached	8.5	19.5	72.0	121	3	Agree
77	In studies of ERBT, the presence of obturator nerve reflex is an important outcome to measure	4.7	25.0	70.3	135	7	Agree	1.8	16.7	81.6	121	7	Agree
78	In studies of ERBT, the need for bladder irrigation is an important outcome to measure	12.2	25.2	62.6	135	4	Not reached	6.0	17.9	76.1	121	4	Agree
79	In studies of ERBT, the duration of urethral catheterisation is an important outcome to measure	11.5	20.8	67.7	135	5	Not reached	8.5	12.0	79.5	121	4	Agree
80	In studies of ERBT, hospital stay is an important outcome to measure	10.5	21.1	68.4	135	2	Not reached	7.6	10.9	81.5	121	2	Agree
81	In studies of ERBT, the complication rate is an important outcome to measure	0	1.5	98.5	135	1	Agree	0	0.8	99.2	121	1	Agree
82	In studies of ERBT, the Clavien-Dindo grading system is the preferred system to measure the severity of complication	2.3	9.4	88.3	135	7	Agree	1.7	5.2	93.0	121	6	Agree
83	In studies of ERBT, the need for blood transfusion is an important outcome to measure	9.8	16.7	73.5	135	3	Agree	5.9	12.6	81.5	121	2	Agree
84	In studies of ERBT, the occurrence of urethral stricture is an important outcome to measure	11.2	22.4	66.4	135	1	Not reached	6.7	15.8	77.5	121	1	Agree
85	In studies of ERBT, the occurrence of bladder perforation is an important outcome to measure	0	2.3	97.7	135	2	Agree	0	1.7	98.3	121	1	Agree
86	In studies of ERBT, the occurrence of urinary tract infection is an important outcome to measure	12.7	27.6	59.7	135	1	Not reached	6.7	20.8	72.5	121	1	Agree
87	In studies of ERBT, the occurrence of transurethral resection syndrome is an important outcome to measure	14.9	23.1	61.9	135	1	Not reached	12.5	15.0	72.5	121	1	Agree
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	18.7	29.1	52.2	135	1	Not reached	10.0	28.3	61.7	121	1	Not reached
89	In studies of ERBT, the occurrence of ureteric stricture is an important outcome to measure	11.2	21.6	67.2	135	1	Not reached	5.8	13.3	80.8	121	1	Agree
90	In studies of ERBT, the successful en bloc resection rate (ie, removal of bladder tumour in one piece) is an important outcome to measure	0.7	3.0	96.3	135	1	Agree	0	0.8	99.2	121	1	Agree
91	In studies of ERBT, presence of detrusor muscle in the ERBT specimen is an important outcome to measure	0.7	2.2	97.0	135	1	Agree	0	2.5	97.5	121	1	Agree

Table 4 (*Continued*)

Domains and statements		Round 1[a]						Round 2[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status	% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
92	In studies of ERBT, presence of clear circumferential resection margin in the ERBT specimen is an important outcome to measure	2.3	5.3	92.5	135	2	Agree	3.3	2.5	94.2	121	1	Agree
93	In studies of ERBT, presence of clear deep resection margin in the ERBT specimen is an important outcome to measure	0	3.7	96.3	135	1	Agree	0	0.8	99.2	121	1	Agree
94	In studies of ERBT, whether postoperative intravesical instillation of chemotherapy is given is an important outcome to report	0.8	15.9	83.3	135	3	Agree	0.8	10.9	88.2	121	2	Agree
95	In studies of ERBT, whether second-look transurethral resection is performed is an important outcome to report	3.0	9.0	88.0	135	2	Agree	1.7	6.7	91.6	121	2	Agree
96	In studies of ERBT, whether any residual disease is detected upon second-look transurethral resection is an important outcome to report	1.5	3.8	94.7	135	2	Agree	0	2.5	97.5	121	2	Agree
97	In studies of ERBT, whether any upstaging of disease is detected upon second-look transurethral resection is an important outcome to report	1.5	4.5	94.0	135	2	Agree	0	3.4	96.6	121	2	Agree
98	In studies of ERBT, whether intravesical BCG therapy is given is an important outcome to report	3.8	18.0	78.2	135	2	Agree	1.7	9.2	89.1	121	2	Agree
99	In studies of ERBT, 3-mo recurrence rate is an important outcome to measure	0.7	4.5	94.8	135	1	Agree	0	1.7	98.3	121	1	Agree
100	In studies of ERBT, 1-yr recurrence rate is an important outcome to measure	0	2.3	97.7	135	2	Agree	0	0.8	99.2	121	1	Agree
101	In studies of ERBT, 1-yr progression rate is an important outcome to measure	0	1.5	98.5	135	1	Agree	0	0.8	99.2	121	1	Agree
102	In studies of ERBT, 5-yr recurrence rate is an important outcome to measure	1.5	6.7	91.8	135	1	Agree	0	2.5	97.5	121	1	Agree
103	In studies of ERBT, 5-year progression rate is an important outcome to measure	1.5	6.0	92.5	135	1	Agree	0	2.5	97.5	121	1	Agree

BCG = bacillus Calmette-Guérin; EAU = European Association of Urology; ERBT = En bloc resection of bladder tumour; TURBT = Transurethral resection of bladder tumour.

[a] In columns showing percentages agree/equivocal/disagree, red shaded cells indicate ≥70%.

[b] Green shaded cell indicate ≥15% of disagree despite ≥70% of agree in the same statement.

[c] This statement was added after first round of Delphi survey.

Table 5 – Summary of the statements that were discussed and re-voted, and their consensus status after the voting session.

Domains and statements		Voting session[a]					
		% Disagree (1–3)	% Equivocal (4–6)	% Agree (7–9)	Total *N*	Unable to score *N*	Consensus status
Definitions and objectives of ERBT							
7	ERBT should be considered for treatment of muscle-invasive bladder cancer	80.0	6.7	13.3	15	0	Disagree
8	ERBT should be considered to treat carcinoma in situ of the bladder to optimise subsequent treatment	73.3	13.3	13.3	15	0	Disagree
Case selection							
11	ERBT is feasible for patients with bladder tumour size of >3 cm	0.0	6.7	93.3	15	0	Agree
12	Number of bladder tumours is a major limitation in performing ERBT	86.7	6.7	6.7	15	0	Disagree
14	If tumour size is not an issue, ERBT is feasible for patients with >4 bladder tumours	0.0	0.0	100.0	15	0	Agree
15	Tumour location is a major limitation in performing ERBT	73.3	20.0	6.7	15	0	Disagree
21	ERBT is feasible for bladder tumour located at the bladder dome	0.0	0.0	100.0	15	0	Agree
Surgical procedure							
25	Narrow-band imaging, Image 1S, or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	20.0	33.3	46.7	15	0	Not reached
31	After ERBT, additional biopsy of the tumour base should be performed routinely	86.7	6.7	6.7	15	0	Disagree
32	After ERBT, additional biopsy of the tumour edge should be performed routinely	100.0	0.0	0.0	15	0	Disagree
Different modalities of ERBT							
46	HybridKnife (hydrodissection) is the safest modality for performing ERBT	86.7	6.7	6.7	15	0	Disagree
47	There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	0.0	21.4	78.6	14	1	Agree
Specimen preparation and reporting of histological findings							
59	For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	40.0	33.3	26.7	15	0	Not reached
60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	20.0	26.7	53.3	15	0	Not reached
Data reporting and outcome measures							
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	13.3	46.7	40.0	15	0	Not reached

ERBT = en bloc resection of bladder tumour.
[a] In columns showing percentages agree/equivocal/disagree, red shaded cells indicate ≥70%.

pearance, size and multifocality, all steps of the procedure, as well as the extent and completeness of resection [54], and these also apply to ERBT. In addition, the modality used for ERBT, success of ERBT, the need of conversion to conventional TURBT, method of tumour extraction, and any additional biopsy of the tumour base and tumour edge must be documented. Any problems encountered during the ERBT procedure, including the occurrence of obturator reflex, bladder perforation, and any difficulty in tumour extraction, must be documented.

3.5.6. *Specimen preparation and reporting of histological findings*

Every ERBT specimen must be prepared and sent for histological assessment separately. The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, and presence of CIS and detrusor muscle [54], and these also apply to ERBT specimens. In addition, the maximal dimension of the bladder tumour [36], T1 substage [55–57], and circumferential and deep resection margins [33,35,46–48] must be assessed.

3.5.7. *Postoperative management and follow-up schedule*

It is safe to give a single dose of immediate intravesical chemotherapy [19,22,29,33,36,37,44,45], to perform second-look TURBT [39,44], and to give intravesical bacillus Calmette-Guérin (BCG) therapy after ERBT [19,33,49]. The indications should follow the EAU guidelines recommendation as in the case of conventional TURBT [54]. The

Table 6 – Final consensus statements on en bloc resection of bladder tumour.

Domains and statements		Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
Definitions and objectives of ERBT			
1	Removal of bladder tumour in one piece is the most appropriate definition for ERBT	Delphi	Agree
2	The depth of ERBT must include the detrusor muscle layer in the specimen	Delphi	Agree
3	One of the main goals of ERBT is to ensure complete local resection of bladder tumour	Delphi	Agree
4	One of the main goals of ERBT is to ensure proper local staging of the disease	Delphi	Agree
5	One of the main goals of ERBT is to reduce the risk of tumour reimplantation	Delphi	Agree
6	ERBT should always be considered for the treatment of non–muscle-invasive bladder cancer	Delphi	Agree
7	ERBT should be considered for the treatment of muscle-invasive bladder cancer	Meeting	Disagree
8	ERBT should be considered for the treatment of carcinoma in situ of the bladder to optimise subsequent treatment	Meeting	Disagree
Case selection			
9	Size of bladder tumour is a major limitation in performing ERBT	Delphi	Agree
10	ERBT is feasible for patients with bladder tumour size of $\leq$3 cm	Delphi	Agree
11	ERBT is feasible for patients with bladder tumour size of $>$3 cm	Meeting	Agree
12	The number of bladder tumours is a major limitation in performing ERBT	Meeting	Disagree
13	If tumour size is not an issue, ERBT is feasible for patients with $\leq$4 bladder tumours	Delphi	Agree
14	If tumour size is not an issue, ERBT is feasible for patients with $>$4 bladder tumours	Meeting	Agree
15	Tumour location is a major limitation in performing ERBT	Meeting	Disagree
16	ERBT is feasible for bladder tumour located at the posterior wall	Delphi	Agree
17	ERBT is feasible for bladder tumour located at the anterior wall	Delphi	Agree
18	ERBT is feasible for bladder tumour located at the right lateral wall	Delphi	Agree
19	ERBT is feasible for bladder tumour located at the left lateral wall	Delphi	Agree
20	ERBT is feasible for bladder tumour located at the trigone	Delphi	Agree
21	ERBT is feasible for bladder tumour located at the bladder dome	Meeting	Agree
22	ERBT is feasible for bladder tumour located at the bladder neck	Delphi	Agree
23	ERBT is feasible for bladder tumour located near the ureteric orifice	Delphi	Agree
Surgical procedure			
24	A thorough cystoscopic examination must be performed before any ERBT	Delphi	Agree
25	Narrow-band imaging, Image 1S, or photodynamic diagnosis must be considered to enhance bladder cancer detection before ERBT	Meeting	Not reached
26	The bladder should be distended enough to facilitate ERBT	Delphi	Agree
27	The bladder should not be overdistended to avoid bladder perforation upon ERBT	Delphi	Agree
28	The planned circumferential margin should be marked first to facilitate subsequent ERBT	Delphi	Agree
29	Upon ERBT, the planned circumferential margin should be at least 5 mm from any visible bladder tumour	Delphi	Agree
30	Upon ERBT, the depth of incision should be made at the detrusor muscle layer	Delphi	Agree
31	After ERBT, additional biopsy of the tumour base should be performed routinely	Meeting	Disagree
32	After ERBT, additional biopsy of the tumour edge should be performed routinely	Meeting	Disagree
33	If bladder tumours are adjacent to each other, en bloc resection of the cluster of bladder tumours as a whole can be considered	Delphi	Agree
34	If the size of bladder tumour is too big, after ERBT, dividing the specimen into 2–3 pieces for retrieval can be considered	Delphi	Agree
35	If any technical difficulty is encountered upon ERBT, conversion to conventional TURBT should be considered	Delphi	Agree
36	Special extraction methods (Endobag, laparoscopic instrument through nephroscope, etc.) can be considered in retrieving large ERBT specimens	Delphi	Agree
Different modalities of ERBT			
37	It is technically feasible to use monopolar energy for ERBT	Delphi	Agree
38	It is technically feasible to use bipolar energy for ERBT	Delphi	Agree
39	It is technically feasible to use holmium laser for ERBT	Delphi	Agree
40	It is technically feasible to use thulium laser for ERBT	Delphi	Agree
41	It is technically feasible to use HybridKnife (hydrodissection) for ERBT	Delphi	Agree
42	ERBT using monopolar energy allows conversion to piecemeal resection readily when technical difficulty arises	Delphi	Agree
43	ERBT using bipolar energy allows conversion to piecemeal resection readily when technical difficulty arises	Delphi	Agree
44	Holmium laser eliminates the risk of obturator nerve reflex during ERBT	Delphi	Agree
45	Thulium laser eliminates the risk of obturator nerve reflex during ERBT	Delphi	Agree
46	HybridKnife (hydrodissection) is the safest modality for performing ERBT	Meeting	Disagree

Table 6 (*Continued*)

Domains and statements		Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
47	There is a risk of residual disease and understaging when we use HybridKnife (hydrodissection) for ERBT due to its nature of submucosal elevation	Meeting	Agree
Reporting of intraoperative findings for patients undergoing ERBT			
48	The modality used for ERBT must be documented	Delphi	Agree
49	Whether ERBT has been successfully performed, or any need of conversion to conventional TURBT, must be documented	Delphi	Agree
50	Whether additional biopsy of the tumour base has been performed must be documented	Delphi	Agree
51	Whether additional biopsy of the tumour edge has been performed must be documented	Delphi	Agree
52	The EAU guidelines stated that the operative record of TURBT must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection. This recommendation should also be applied to ERBT	Delphi	Agree
53	Any occurrence of obturator nerve reflex and the laterality of obturator nerve reflex being encountered during ERBT must be documented	Delphi	Agree
54	Any occurrence of extraperitoneal or intraperitoneal bladder perforation during ERBT must be documented	Delphi	Agree
55	The method of tumour extraction must be documented	Delphi	Agree
56	Any difficulty in tumour extraction must be documented	Delphi	Agree
57	Whether the ERBT specimen has been divided for extraction must be documented	Delphi	Agree
Specimen preparation and reporting of histological findings			
58	Every ERBT specimen must be prepared and sent for histological assessment separately	Delphi	Agree
59	For the ERBT specimen, the circumferential mucosal edge must be pinned for better orientation and better histological assessment of the bladder tumour	Meeting	Not reached
60	For the ERBT specimen, the circumferential and deep resection margins must be inked to facilitate subsequent histological assessment	Meeting	Not reached
61	For the ERBT specimen, it should be serially sectioned at 2 mm intervals	Delphi	Agree
62	The EAU guidelines stated that the pathological report of TURBT specimen should specify tumour location, tumour grade and stage, lymphovascular invasion, unusual (variant) histology, and presence of carcinoma in situ and detrusor muscle. This recommendation should also apply to ERBT specimen	Delphi	Agree
63	Upon histological assessment of the ERBT specimen, the maximal dimension of bladder tumour must be documented	Delphi	Agree
64	Upon histological assessment of the ERBT specimen, T1 substage must be assessed	Delphi	Agree
65	Upon histological assessment of the ERBT specimen, circumferential resection margin must be assessed	Delphi	Agree
66	Upon histological assessment of the ERBT specimen, deep resection margin must be assessed	Delphi	Agree
Postoperative management and follow-up schedule			
67	It is safe to give a single dose of intravesical chemotherapy immediately after ERBT	Delphi	Agree
68	Indications of a single dose of intravesical chemotherapy immediately after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
69	It is safe to perform second-look TURBT after the first ERBT	Delphi	Agree
70	The indications of second-look TURBT after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
71	It is safe to give intravesical BCG therapy after ERBT	Delphi	Agree
72	Indications of intravesical BCG therapy after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
73	The flexible cystoscopy surveillance protocol after ERBT should follow the EAU guidelines recommendation as in the case of conventional TURBT	Delphi	Agree
74[a]	Upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in-field and out-of-field recurrence	Delphi	Agree
Data reporting and outcome measures			
75	In studies of ERBT, both per-patient and per-tumour analyses should be performed for different outcomes	Delphi	Agree
76	In studies of ERBT, the operative time is an important outcome to measure	Delphi	Agree
77	In studies of ERBT, the presence of obturator nerve reflex is an important outcome to measure	Delphi	Agree
78	In studies of ERBT, the need for bladder irrigation is an important outcome to measure	Delphi	Agree
79	In studies of ERBT, the duration of urethral catheterisation is an important outcome to measure	Delphi	Agree
80	In studies of ERBT, hospital stay is an important outcome to measure	Delphi	Agree
81	In studies of ERBT, the complication rate is an important outcome to measure	Delphi	Agree

Table 6 (*Continued*)

Domains and statements		Consensus stage (Delphi/meeting)	Direction of consensus (agree/disagree)
82	In studies of ERBT, the Clavien-Dindo grading system is the preferred system to measure the severity of complication	Delphi	Agree
83	In studies of ERBT, the need for blood transfusion is an important outcome to measure	Delphi	Agree
84	In studies of ERBT, the occurrence of urethral stricture is an important outcome to measure	Delphi	Agree
85	In studies of ERBT, the occurrence of bladder perforation is an important outcome to measure	Delphi	Agree
86	In studies of ERBT, the occurrence of urinary tract infection is an important outcome to measure	Delphi	Agree
87	In studies of ERBT, the occurrence of transurethral resection syndrome is an important outcome to measure	Delphi	Agree
88	In studies of ERBT, the occurrence of urinary retention is an important outcome to measure	Meeting	Not reached
89	In studies of ERBT, the occurrence of ureteric stricture is an important outcome to measure	Delphi	Agree
90	In studies of ERBT, the successful en bloc resection rate (ie, removal of bladder tumour in one piece) is an important outcome to measure	Delphi	Agree
91	In studies of ERBT, presence of detrusor muscle in the ERBT specimen is an important outcome to measure	Delphi	Agree
92	In studies of ERBT, presence of clear circumferential resection margin in the ERBT specimen is an important outcome to measure	Delphi	Agree
93	In studies of ERBT, presence of clear deep resection margin in the ERBT specimen is an important outcome to measure	Delphi	Agree
94	In studies of ERBT, whether postoperative intravesical instillation of chemotherapy is given is an important outcome to report	Delphi	Agree
95	In studies of ERBT, whether second-look transurethral resection is performed is an important outcome to report	Delphi	Agree
96	In studies of ERBT, whether any residual disease is detected upon second-look transurethral resection is an important outcome to report	Delphi	Agree
97	In studies of ERBT, whether any upstaging of disease is detected upon second-look transurethral resection is an important outcome to report	Delphi	Agree
98	In studies of ERBT, whether intravesical BCG therapy is given is an important outcome to report	Delphi	Agree
99	In studies of ERBT, 3-mo recurrence rate is an important outcome to measure	Delphi	Agree
100	In studies of ERBT, 1-yr recurrence rate is an important outcome to measure	Delphi	Agree
101	In studies of ERBT, 1-yr progression rate is an important outcome to measure	Delphi	Agree
102	In studies of ERBT, 5-yr recurrence rate is an important outcome to measure	Delphi	Agree
103	In studies of ERBT, 5-yr progression rate is an important outcome to measure	Delphi	Agree

BCG = bacillus Calmette-Guérin; EAU = European Association of Urology; ERBT = en bloc resection of bladder tumour; TURBT = transurethral resection of bladder tumour.
[a] This statement was added after first round of Delphi survey.

flexible cystoscopy surveillance protocol after ERBT should also follow the EAU guidelines recommendation as in the case of conventional TURBT [54]. In addition, upon flexible cystoscopy, the location of tumour recurrence must be documented to help differentiate between in- and out-of-field recurrence [19,34,37].

3.5.8. *Data reporting and outcome measures*

In studies of ERBT, both per-patient and -tumour analyses should be performed for different outcomes as appropriate [46,47]. Perioperative outcomes, including operative time, obturator nerve reflex, successful en bloc resection rate, need of bladder irrigation, duration of urethral catheterisation, and hospital stay, should be documented. Severity of complications should be measured using the Clavien-Dindo grading system [58]. Complications including bladder perforation, need of blood transfusion, ureteric stricture, urethral stricture, urinary tract infection, and transurethral resection syndrome should be documented. For the histological assessment, presence of detrusor muscle, and circumferential and deep resection margins are important outcomes to measure. Whether adjunct treatments, including postoperative intravesical instillation of chemotherapy, second-look TURBT, and intravesical BCG therapy, have been given or performed should be reported. For those with second-look TURBT performed, any residual disease or upstaging of disease should be reported. For the oncological outcomes, 3-mo recurrence rate, 1-yr recurrence and progression rates, and 5-yr recurrence and progression rates are important outcomes to measure.

4. Discussion

In our effectiveness review, which is the most comprehensive and methodologically robust systematic review of the ERBT evidence base to date, we identified 10 RCTs comparing ERBT and TURBT; however, only four of them [19,22,29,31] were published as full-text articles. High-

quality data are limited for making robust recommendations in ERBT, and this explains why it is important to develop a consensus statement to provide the highest level of evidence that we can achieve so far, which can serve as a standard reference for health care professionals in the future. This consensus statement is the first attempt in trying to standardise the management of bladder cancer patients with special focus on ERBT. We mobilised the international community and used transparent and robust methods to review the evidence, identify current uncertainties, and survey expert opinion in an unbiased way, in order to provide recommendations for interim practice guidance and a basis to inform the research agenda. Health care professionals from different specialities (ie, urologists, oncologists, and pathologists) were involved to ensure that we had a comprehensive collection of opinions across different fields.

4.1. Relevance and impact of study findings on clinical practice and research

There are several important messages that may impact our clinical practice. Although tumour size has long been recognised as a major limitation, we must emphasise that ERBT is a treatment intended for patients with NMIBC. In patients with bladder tumours larger than 3 cm, there is a reasonable chance of MIBC, and ERBT should not be considered a definitive treatment when there is a suspicion of MIBC. Moreover, it is recognised that the major benefit of ERBT is the ability to ensure a complete local resection, and this holds true even when the specimen cannot be retrieved in one piece. Therefore, we should still consider ERBT in patients with large bladder tumours where NMIBC is considered a possibility. We also offered practical solutions on how we can extend the indication of ERBT to patients with large bladder tumours. Modified ERBT, for example, en bloc resection followed by division of specimen into two to three pieces for retrieval, is considered acceptable [45,49]. The use of special tumour extraction methods may also facilitate tumour extraction [50], but we need to be aware that the devices being used implied additional costs and were not formally approved for such indication, and whether they would lead to increased risk of complications such as urethral stricture is unknown. There is an urgent need for innovative methods of tumour extraction so as to achieve a true ERBT even for large bladder tumours.

ERBT is a surgical approach that aims to uphold the basic oncological principles in bladder cancer resection. Although there are different modalities of ERBT, they are all technically feasible and there are no data showing superiority of one over the other. In ERBT, surgical technique is primary and tools are secondary. Of note, bipolar ERBT appears to be the most acceptable modality based on the percentage of agreement. This might be explained by its widespread availability, ease and precision of resection, as well as the allowance of instant conversion to conventional TURBT. Although there is a risk of residual disease and understaging when using HybridKnife (hydrodissection) for ERBT, this is only theoretical based on its nature of submucosal elevation and whether this is genuinely true is unknown.

As ERBT specimens allow assessment of the depth of invasion as well as the resection margins, routine additional biopsy of tumour base and tumour edge after ERBT is considered unnecessary. If there is any doubt regarding the completeness of resection, additional resection of tumour base and edge can be considered, and they should be sent for histological assessment separately. Although pinning of circumferential mucosal margin and inking of resection margins in ERBT specimens are commonly performed (and possibly a good practice), it is not considered mandatory for a proper histological assessment. ERBT specimens also allow more precise assessment of the T1 substage. World Health Organization's classification of T1a–c disease is considered acceptable [57], but more research work will be needed to see whether they carry any important prognostic implications in NMIBC after ERBT.

We noticed a significant variation in the reporting of outcome measures across nonrandomised studies and RCTs. Data on important outcomes such as the presence of detrusor muscle were not readily reported in RCTs. There is also a wide variation in the study quality, as reflected by our risk of bias assessment. Standardisation on data reporting and outcome measures is important to move ERBT forward. Future studies on ERBT should consider incorporating the important outcome measures as identified by our consensus statement.

4.2. Strengths and limitations

This consensus statement was developed using a robust and reproducible method [10,14–16]. Our systematic reviews were conducted according to the PRISMA guidelines [2]. When compared with previous meta-analyses in the literature [59–62], our search strategy was most comprehensive, and we included only RCTs with a proper risk of bias assessment in our meta-analysis. The GRADE method was used for assessing certainty of evidence [9], and this is useful for decision making at many levels, including for the development of clinical practice guidelines. Our uncertainties review also provided a solid basis for the survey items being developed. Invitations were sent to a large panel of health care professionals purposively sampled from across the world. The consensus building process was based on a two-round Delphi survey, followed by a consensus panel meeting, where anonymous voting techniques were used. All these improved the internal and external validity of the study results. The definition of a consensus was also based on previously described methodology.

There are several limitations in this study. First, we recognise the lack of high-quality studies in ERBT. We were also not able to stratify the results according to patient and disease factors. Therefore, some results of the effectiveness review (eg, recurrence rates) have to be interpreted with caution. Second, statements generated were brief, concise, and binary in nature. Areas of uncertainty that are complex in nature may not be addressed adequately. Some terminologies (eg, degree of bladder distension) were also

difficult to define. Third, most of the participants involved were urologists, and they might lack knowledge regarding certain aspects of ERBT such as reporting of histological findings. The statements generated had an extensive coverage of every surgical aspect of ERBT. Even urologists may not have sufficient personal experience to vote in every statement (eg, different modalities of ERBT). Fourth, we recognised that there was strong representation from Europe and Asia in the Delphi survey. This may represent a selection bias from purposive sampling, and the results may not be applicable to regions outside Europe and Asia. On the contrary, it may reflect a genuine situation that ERBT is much more commonly practised in Europe and Asia.

4.3. Future directions of ERBT

To determine whether ERBT should replace conventional TURBT as the standard of care will require more results from high-quality RCTs. In our systematic review, we noticed that a number of RCTs have been presented but not fully published. Proper reporting according to the CONSORT statement is strongly encouraged [63]. There are also a number of on-going RCTs with clinically important primary outcomes. The EB-StaR study is a multicentre study comparing the 1-yr recurrence rates between bipolar ERBT and bipolar conventional TURBT for patients with bladder tumour size of $\leq$3 cm [64]. There are two RCTs comparing between laser ERBT and conventional TURBT with the primary outcome of residual tumour upon second TURBT [65,66]. There is another RCT investigating the presence of detrusor muscle in the specimen, which may serve as a surrogate marker for the quality of resection [67].

One of the major criticisms of ERBT is the inability to retrieve large bladder tumours in one piece. Acknowledging the benefit of ensuring a complete resection, we should accept modified approaches of ERBT (eg, ERBT followed by retrieval of bladder tumour in several pieces [45,49], piecemeal resection of the exophytic part of bladder tumour followed by en bloc resection of the tumour base [68], etc.). Moreover, ERBT is focused on patients with NMIBC (presumably smaller in size in most cases), so a true ERBT is still feasible for the majority of the patients. An exploratory study investigating the role of modified ERBT for patients with bladder tumour size of $\geq$3 cm is currently under way [69].

Although ERBT is a promising surgical technique for NMIBC, the learning curve of ERBT and whether it can easily be generalised is an important issue to address. More effort will be needed for proper education and training globally. With the foundation of the consensus statement, a prospective international registry study on ERBT is planned. This will provide us with more insights into the generalisability and practicality of implementing ERBT in our clinical practice. Long-term real-world data will also be useful in determining the true value of ERBT. We believe that oncological principles exist for good reasons, and our group will continue to work together and contribute to the development of ERBT in a collaborative manner.

5. Conclusions

A consensus statement for ERBT has been developed, and it has a comprehensive coverage regarding every aspect of ERBT. The findings will guide and inform health care professionals about the routine clinical practice of ERBT, and has important implications regarding future studies of ERBT. The consensus statement will serve as a standard of reference until higher level of evidence from prospective RCTs is available.

Author contributions: Marek Babjuk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Teoh, MacLennan, Mostafid, Herrmann, Babjuk.
Acquisition of data: Teoh, MacLennan, V.W.-S. Chan, Yuan, Yu.
Analysis and interpretation of data: Teoh, MacLennan, V.W.-S. Chan, Kramer, Malavaud, Mostafid, Herrmann, Babjuk.
Drafting of the manuscript: Teoh, MacLennan, Mostafid, Herrmann, Babjuk.
Critical revision of the manuscript for important intellectual content: Miki, H.-Y. Lee, Chiong, L.-S. Lee, Yong, Chow, Poon, R. Chan, Lai, Breda, Kramer, Malavaud.
Statistical analysis: MacLennan, V.W.-S. Chan, Yuan.
Obtaining funding: Teoh, Ng.
Administrative, technical, or material support: Teoh, Ng.
Supervision: MacLennan, Babjuk.
Other: None.

Financial disclosures: Marek Babjuk certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Jeremy Yuen-Chun Teoh has received honorarium from Olympus and Boston Scientific, travel grants from Olympus and Boston Scientific, and research grants from Olympus and Storz. Bernard Malavaud has received research grant from Cepheid, and is a consultant for and has received honorarium from Cephied and Olympus. Hugh Mostafid has received honorarium from Olympus. Thomas Herrmann has received travel grants from Karl Storz and LISA Laser, and is a consultant for Karl Storz and Boston Scientific. Marek Babjuk has received honorarium from Olympus and Ipsen.

Funding/Support and role of the sponsor: This study was supported by the General Research Fund/Early Career Scheme of the Research Grants Council, Hong Kong, China (reference no. 24116518).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.04.059.

References

[1] Kitamura K, Kataoka K, Fujioka H, Kashiwai K. Transurethral resection of a bladder tumor by the use of a polypectomy snare. J Urol 1980;124:808–9.

[2] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[3] Teoh J, Yuan Y, Babjuk M, Herrmann T, Mostafid H, MacLennan S. A protocol for a systematic review of a) the clinical effectiveness of 'en bloc' compared to conventional 'piecemeal' transurethral resection in non muscle invasive bladder cancer tumors and b) clinical and technical uncertainties in the en bloc procedure. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=139809.
[4] Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol 2017;87:4–13.
[5] Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.
[6] Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. Chichester, UK: John Wiley & Sons; 2011.
[7] Knoll T, Omar MI, Maclennan S, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the European Association of Urology. Eur Urol 2018;73:290–300.
[8] Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
[9] Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook. https://gdt.gradepro.org/app/handbook/handbook.html.
[10] Williamson PR, Altman DG, Bagley H, et al. The COMET handbook: version 1.0. Trials 2017;18(Suppl 3):280.
[11] Comet Initiative DelphiManager, 2011–2015. http://www.comet-initiative.org/delphimanager/index.html.
[12] Gudaru K, Blanco LT, Castellani D, et al. Connecting the urological community: the #UroSoMe experience. J Endoluminal Endourol 2019;2:e20–9.
[13] MacLennan S, Kirkham J, Lam TBL, Williamson PR. A randomized trial comparing three Delphi feedback strategies found no evidence of a difference in a setting with high initial agreement. J Clin Epidemiol 2018;93:1–8.
[14] Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multistakeholder effort: under the auspices of the EAU-ESMO Guidelines Committees. Eur Urol 2019;30:1697–727.
[15] Horwich A, Babjuk M, Bellmunt J, et al. EAU-ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees. Ann Oncol 2019;30:1697–727.
[16] Lam TBL, MacLennan S, Willemse PM, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE study). Eur Urol 2019;76:790–813.
[17] De Meyer D, Kottner J, Beele H, et al. Delphi procedure in core outcome set development: rating scale and consensus criteria determined outcome selection. J Clin Epidemiol 2019;111:23–31.
[18] Poll Everywhere. https://www.polleverywhere.com.
[19] Balan GX, Geavlete PA, Georgescu DA, et al. Bipolar en bloc tumor resection versus standard monopolar TURBT—which is the best way to go in non-invasive bladder cancer? Rom J Morphol Embryol 2018;59:773–80.
[20] Geavlete B, Ene C, Bulai C, Balan G, Geavlete P. Medium size bladder tumors' en-block bipolar ablation put to the test-a long term, prospective, randomized-controlled clinical comparison to standard resection. J Urol 2018;199(4 Suppl 1):e97–8.
[21] Geavlete B, Multescu R, Georgescu D, et al. Bipolar en bloc tumor resection versus standard monopolar TURBT in non-muscle invasive bladder cancer—a medium-term, prospective, randomized-controlled comparison. Eur Urol Suppl 2019;18:e761.
[22] Chen X, Liao J, Chen L, et al. En bloc transurethral resection with 2-micron continuous-wave laser for primary non-muscle-invasive bladder cancer: a randomized controlled trial. World J Urol 2015;33:989–95.
[23] Cheng Y, Qu W, Sun Y, Li J, Liang L. Transurethral endoscopic submucosal en blot dissection for non-muscle invasive bladder tumor: a prospective comparison study of HybridKnife assisted versus conventional dissection technique. J Urol 2016;195(4 Suppl. 1):e289.
[24] Gakis G, Karl A, Bertz S, et al. Transurethral en-bloc hydrodissection for non-muscle invasive bladder cancer: results of a randomized controlled trial. Eur Urol Suppl 2017;16:e1143–4.
[25] Hu J, Song X, Yu X, Wang S. En Bloc transurethral resection with hybrid knife for treatment primary non-muscle-invasive bladder cancer: a single-center, randomized, controlled trial. J Endourol 2017;31(Suppl 2):A257.
[26] Hu J. En bloc transurethral resection with hybrid knife for treatment primary non-muscle-invasive bladder cancer: a single-center, controlled trial based on pathological staging. J Urol 2018;199(4 Suppl 1):e615.
[27] Kufner M, Decristoforo A, Nicklas A, Walcher U, Herrmann TRW, Nagele U. The new kid on the block: a randomized study comparing waterjet hydrodissection with TURB in the treatment of bladder tumors. Eur Urol Suppl 2014;13:e1108.
[28] Li X, Shao J. Randomized controlled trial comparing standard TUR and en bloc TUR in the patients with non-muscle-invasive urothelial carcinoma of bladder. Int J Urol 2014;21(Suppl 2):A232.
[29] Liu H, Wu J, Xue S, et al. Comparison of the safety and efficacy of conventional monopolar and 2-micron laser transurethral resection in the management of multiple nonmuscle-invasive bladder cancer. J Int Med Res 2013;41:984–92.
[30] Ruffo A, Iacono F, Romis L, et al. Comparing thulium laser en-bloc enucleation and trans-urethral resection in the treatment of non-muscle-invasive bladder cancer. Anticancer Res 2017;37:2111–2.
[31] Zhang XR, Feng C, Zhu WD, et al. Two micrometer continuous-wave thulium laser treating primary non-muscle-invasive bladder cancer: is it feasible? A randomized prospective study. Photomed Laser Surg 2015;33:517–23.
[32] Ukai R, Kawashita E, Ikeda H. A new technique for transurethral resection of superficial bladder tumor in 1 piece. J Urol 2000;163:878–9.
[33] D'Souza N, Verma A. Holmium laser transurethral resection of bladder tumor: our experience. Urol Ann 2016;8:439–43.
[34] Cheng B, Qiu X, Li H, Yang G. The safety and efficacy of front-firing green-light laser endoscopic en bloc photoselective vapo-enucleation of non-muscle-invasive bladder cancer. Ther Clin Risk Manag 2017;13:983–8.
[35] Cheng YY, Sun Y, Li J, et al. Transurethral endoscopic submucosal en bloc dissection for nonmuscle invasive bladder cancer: a comparison study of HybridKnife-assisted versus conventional dissection technique. J Cancer Res Ther 2018;14:1606–12.
[36] Xu H, Ma J, Chen Z, et al. Safety and efficacy of en bloc transurethral resection with 1.9 micron Vela laser for treatment of non-muscle-invasive bladder cancer. Urology 2018;113:246–50.
[37] Zhang KY, Xing JC, Li W, Wu Z, Chen B, Bai DY. A novel transurethral resection technique for superficial bladder tumor: retrograde en bloc resection. World J Surg Oncol 2017;15:125.
[38] Hayashida Y, Miyata Y, Matsuo T, et al. A pilot study to assess the safety and usefulness of combined transurethral endoscopic muco-

sal resection and en-bloc resection for non-muscle invasive bladder cancer. BMC Urol 2019;19:56.
[39] Hurle R, Casale P, Lazzeri M, et al. En bloc re-resection of high-risk NMIBC after en bloc resection: results of a multicenter observational study. World J Urol 2020;38:703–8.
[40] Hurle R, Lazzeri M, Buffi N, et al. PD11-02 En bloc resection of bladder tumours (ERBT): multivariable analysis for prediction of recurrence at mid-term follow-up. J Urol 2016;195:e287–8.
[41] Hurle R, Lazzeri M, Colombo P, et al. "En bloc" resection of non-muscle invasive bladder cancer: a prospective single-center study. Urology 2016;90:126–30.
[42] Hurle R, Lazzeri M, Saita A, et al. Long-term follow-up in high risk non muscle invasive bladder cancer (NMIBC) "en-bloc" resection. Eur Urol Suppl 2018;17:e1063.
[43] Hurle R, Saita A, Lazzeri M, et al. "En bloc" thulium laser resection of NMIBC: technique and preliminary results. Eur Urol Suppl 2018;17:e1966.
[44] Li K, Xu Y, Tan M, Xia S, Xu Z, Xu D. A retrospective comparison of thulium laser en bloc resection of bladder tumor and plasmakinetic transurethral resection of bladder tumor in primary non-muscle invasive bladder cancer. Lasers Med Sci 2019;34:85–92.
[45] Chen J, Zhao Y, Wang S, et al. Green-light laser en bloc resection for primary non-muscle-invasive bladder tumor versus transurethral electroresection: a prospective, nonrandomized two-center trial with 36-month follow-up. Lasers Surg Med 2016;48:859–65.
[46] Teoh JY, Chan ES, Cheng BK, et al. Transurethral en bloc resection versus standard resection of bladder tumour: a prospective comparison on early operative and pathological outcomes. BJU Int 2017;119(Suppl 3):14.
[47] Teoh JYC, Chan E, Cheng KC, et al. Detrusor muscle sampling rate after transurethral en bloc vs standard resection of bladder tumour. Int J Urol 2017;24(Suppl 1):32.
[48] Kramer MW, Rassweiler JJ, Klein J, et al. En bloc resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical en bloc transurethral resection of bladder tumor. World J Urol 2015;33:1937–43.
[49] Sureka SK, Agarwal V, Agnihotri S, Kapoor R, Srivastava A, Mandhani A. Is en-bloc transurethral resection of bladder tumor for non-muscle invasive bladder carcinoma better than conventional technique in terms of recurrence and progression? A prospective study. Indian J Urol 2014;30:144–9.
[50] Naselli A, Introini C, Germinale F, Spina B, Puppo P. En bloc transurethral resection of bladder lesions: a trick to retrieve specimens up to 4.5 cm. BJU Int 2012;109:960–3.
[51] Jiang Y, Lo RK, Lu ZQ, Cheng XB, Xiong L. A novel technique improvement: en bloc resection with an conventional bipolar needle electrode for the treatment of bladder cancer. Surg Pract 2018;22(Suppl 1):54.
[52] Xishuang S, Deyong Y, Xiangyu C, et al. Comparing the safety and efficiency of conventional monopolar, plasmakinetic, and holmium laser transurethral resection of primary non-muscle invasive bladder cancer. J Endourol 2010;24:69–73.
[53] Teoh JYC, Herrmann TRW, Babjuk M. Re: Valeria Panebianco, Yoshifumi Narumi, Ersan Altun, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol 74, 2018, 294–306. Eur Urol 2019;75:e27–8.
[54] Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447–61.
[55] Liang H, Yang T, Wu K, He D, Fan J. En bloc resection improves the identification of muscularis mucosae in non-muscle invasive bladder cancer. World J Urol 2019;37:2677–82.
[56] Yanagisawa T, Miki J, Yorozu T, et al. Clinical efficacy of sub-staging and en-bloc TUR specimen for PT1 bladder cancer. J Urol 2018;199(4 Suppl 1):e1119–20.
[57] Moch H, Humphrey PA, Ulbright TM, Reuter VE. WHO classification of tumours of the urinary system and male genital organs. Lyon, France: International Agency for Research on Cancer; 2016.
[58] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[59] Teng JF, Wang K, Yin L, et al. Holmium laser versus conventional transurethral resection of the bladder tumor. Chin Med J 2013;126:1761–5.
[60] Wu YP, Lin TT, Chen SH, et al. Comparison of the efficacy and feasibility of en bloc transurethral resection of bladder tumor versus conventional transurethral resection of bladder tumor: a meta-analysis. Medicine (Baltimore) 2016;95:e5372.
[61] Zhang D, Yao L, Yu S, et al. Safety and efficacy of en bloc transurethral resection versus conventional transurethral resection for primary nonmuscle-invasive bladder cancer: a meta-analysis. World J Surg Oncol 2020;18:4.
[62] Yang H, Lin J, Gao P, et al. Is the En Bloc Transurethral Resection More Effective than Conventional Transurethral Resection for Non-Muscle-Invasive Bladder Cancer? A Systematic Review and Meta-Analysis. Urol Int 2020;1–8.
[63] Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94.
[64] U.S. National Library of Medicine. Transurethral en bloc versus standard resection of bladder tumour. https://clinicaltrials.gov/ct2/show/NCT02993211.
[65] U.S. National Library of Medicine. Laser en bloc resection of bladder tumor (HoLERBT) vs. conventional transurethral resection of bladder tumors (cTURBT) (HoLERBT). https://clinicaltrials.gov/ct2/show/NCT02555163.
[66] U.S. National Library of Medicine. A study of comparing effects of thulium laser en bloc resection and electrical transurethral resection of the non-muscle invasive bladder cancer. https://clinicaltrials.gov/ct2/show/NCT02951078.
[67] U.S. National Library of Medicine. En-bloc vs conventional resection of primary bladder tumor (eBLOC). https://clinicaltrials.gov/ct2/show/NCT03718754.
[68] Zhang K, Xing J, Li W, Wu Z. A novel transurethral resection technique for superficial bladder tumor: retrograde en bloc resection. J Endourol 2017;31(Suppl 2):A254–5.
[69] U.S. National Library of Medicine. Transurethral modified en bloc resection for large bladder tumours. https://clinicaltrials.gov/ct2/show/NCT04081246.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 546–569 of this issue

En Bloc Resection of Bladder Tumors: Style or Substance?

Dominic C. Grimberg, Ankeet Shah, Brant A. Inman *

Division of Urology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Transurethral en bloc resection of non–muscle-invasive bladder tumor (ERBT) has increased in popularity over recent years, especially in Europe and Asia. While it is not a new concept, the reinvigorated interest in the technique stems from potential areas for improvement over conventional transurethral resection of bladder tumor (TURBT) and supporters quote three main advantages. First, ERBT is thought to improve the quality of histopathological specimens allowing pathologists to better assess margin status for completeness of resection and depth of invasion [1,2]. Second, the more controlled resection may decrease the risk of adverse events such as bladder perforation [3]. Third, the reduction in tumor fracturing leads to fewer floating tumor cells, theoretically reducing the risk of intravesical tumor seeding and improving recurrence rates [1,4]. Unfortunately, high-quality data on ERBT are lacking and available studies are hampered by a lack of standardization for patient selection, technique, and outcomes measured. With little guidance in this space, Teoh et al [5] attempt to shine light on the role of ERBT using a combination of systematic review and expert opinion in this issue of *European Urology*.

Although multiple systematic reviews comparing ERBT and TURBT already exist, the current work is comprehensive and uses robust methodology in accordance with the Cochrane Handbook [1,3,6]. It includes only randomized controlled trial (RCT) data and excludes observational studies in an attempt to reduce selection bias for ERBT. While RCTs generally represent good evidence, they are limited by their restrictive inclusion criteria, which often limit generalizability to the population at large. In the present study, ten RCTs involving a total of 1155 patients (586 ERBT vs 569 TURBT) were identified but, owing to differences in outcome reporting, only a subset of these studies contribute to the pooled outcomes. The authors report fewer bladder perforations and shorter irrigation time with ERBT, but these outcomes were only reported in five ($n = 723$) and two ($n = 195$) trials, respectively. In addition, it is uncertain if the lower perforation rates for ERBT are related to surgeon comfort with the novel technique as early adapters and whether widespread use would show similar results. Similarly, the authors note equivalent recurrence rates at 0–12, 13–24, and 25–36 mo, but only five ($n = 622$), two ($n = 262$), and three ($n = 570$) studies respectively, included these outcomes and the data are unfortunately too limited for subgroup analyses between ERBT modalities or patient and disease factors. The authors include GRADE summaries of data for each outcome, which illustrate the overall poor study quality, as most have low and very low certainty evidence, even when randomized [7].

The main novel contribution of the paper is a qualitative process whereby the authors compiled 99 statements and presented them to a panel of experts for consensus development. The fact that a consensus process is required to interpret the existing ERBT data highlights how poor these data really are. That being said, the inclusion of statements addressing how trials should be designed and reported could lead to improvements in future studies. An additional concern is the constitution of the expert panel: members were chosen either as authors of ERBT systematic reviews or as respondents to an online advertisement with verified personal ERBT experience. Consequently, the panel is heavily skewed towards urologists practicing in Europe and Asia who are early adopters and "believers" in ERBT. The inclusion of statements covering multiple areas from surgical technique to histological preparation also led to grading of statements outside participants' expertise

DOI of original article: https://doi.org/10.1016/j.eururo.2020.04.059.
* Corresponding author. Division of Urology, Duke University Medical Center, 3007 Snyderman Building, 905 La Salle Street, Durham, NC 27710, USA. Tel.: +1 919 6841322, Fax: +1 919 6687093.
E-mail address: brant.inman@duke.edu (B.A. Inman).

https://doi.org/10.1016/j.eururo.2020.05.019

(eg, urologists opining on histology, pathologists opining on surgery). The authors attempt to address with an "unable to score" option, but this was underutilized and no assessment of differences between stakeholder groups was performed.

The main ERBT benefit is avoidance of the piecemeal resection of TURBT that is thought to lead to seeding of normal urothelium by tumor cells shed during resection [1–3]. The existing evidence does not support the notion that ERBT reduces recurrences. In addition, ERBT may not be appropriate for many bladder tumors, including tumors >3 cm, highly multifocal tumors, flat tumors, and tumors at the dome. Specimen retrieval can also be a limitation, as a nicely resected en bloc tumor might be impossible to extract intact through the resectoscope sheath without additional equipment (which is not routinely available).

Overall, this work does provide interim guidance within a growing field and hopefully will standardize care and allow for stronger future studies. However, the consensus statements must be interpreted with caution given the low quality of data on which they are based and the biased constitution of the opinion panel. Unanswered questions remain and Teoh et al reference an additional five ongoing trials that seek to address these issues, although their outcomes are not standardized. We look forward to seeing these results and hope that the unappreciated surgical technique that is TURBT will improve for our patients.

Conflicts of interest: BAI is a consultant/advisor for Ferring Pharmaceuticals, Combat Medical, and Taris Biomedical, and has participated in scientific studies/trials with FKD Therapies, Anchiano Therapeutics, Genentech Inc., Nucleix, Bristol-Myers-Squibb, and Abbott Laboratories. The remaining authors have nothing to disclose.

Acknowledgments: DCG is funded by a Urology Care Foundation Residency Research Award.

References

[1] Mori K, D'Andrea D, Enikeev DV, Egawa S, Shariat SF. En bloc resection for nonmuscle invasive bladder cancer: review of the recent literature. Curr Opin Urol 2020;30:41–7.

[2] Kramer MW, Altieri V, Hurle R, et al. Current evidence of transurethral en-bloc resection of nonmuscle invasive bladder cancer. Eur Urol Focus 2017;3:567–76.

[3] Yang H, Lin J, Gao P, et al. Is the en bloc transurethral resection more effective than conventional transurethral resection for non-muscle-invasive bladder cancer? A systematic review and meta-analysis. Urol Int 2020.

[4] Kramer MW, Rassweiler JJ, Klein J, et al. En bloc resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical en bloc transurethral resection of bladder tumor. World J Urol 2015;33:1937–43.

[5] Teoh JYC, MacLennan S, Chan VWS, et al. An international collaborative consensus statement on en bloc resection of bladder tumour incorporating two systematic reviews, a two-round Delphi survey, and a consensus meeting. Eur Urol 2020;78:546–69.

[6] Zhang D, Yao L, Yu S, et al. Safety and efficacy of en bloc transurethral resection versus conventional transurethral resection for primary nonmuscle-invasive bladder cancer: a meta-analysis. World J Surg Oncol 2020;18:4.

[7] Schunemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group; 2013.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Reconstructive Urology

Editorial by Nadir I. Osman and Christopher R. Chapple on pp. 581–582 of this issue

Surgical Treatment for Recurrent Bulbar Urethral Stricture: A Randomised Open-label Superiority Trial of Open Urethroplasty Versus Endoscopic Urethrotomy (the OPEN Trial)

Beatriz Goulao [a], Sonya Carnell [b], Jing Shen [c], Graeme MacLennan [d], John Norrie [e], Jonathan Cook [f], Elaine McColl [c], Matt Breckons [c], Luke Vale [c,], Paul Whybrow [g], Tim Rapley [h], Rebecca Forbes [b], Stephanie Currer [b], Mark Forrest [d], Jennifer Wilkinson [b], Daniela Andrich [i], Stewart Barclay [j], Anthony Mundy [i], James N'Dow [k], Stephen Payne [l], Nick Watkin [m], Robert Pickard [n,†]*

[a] *Health Services Research Unit, University of Aberdeen, Aberdeen, UK;* [b] *Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK;* [c] *nstitute of Health and Society, Newcastle University, Newcastle upon Tyne, UK;* [d] *Centre for Healthcare and Randomised Trials, University of Aberdeen, Aberdeen, UK;* [e] *Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, UK;* [f] *Centre for Statistics in Medicine, University of Oxford, Oxford, UK;* [g] *Hull York Medical School, University of Hull, Hull, UK;* [h] *Social Work, Education and Community Wellbeing, University of Northumbria, Newcastle upon Tyne, UK;* [i] *University College London Hospital, London, UK;* [j] *Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK;* [k] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [l] *Central Manchester Hospitals NHS Foundation Trust, Manchester, UK;* [m] *St George's University Hospitals NHS Foundation Trust, London, UK;* [n] *Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK*

Article info

Article history:
Accepted June 2, 2020

Associate Editor:
James Catto

Stats Editor:
Melissa Assel

Keywords:
Surgery
Randomised controlled trial
Urethral stricture
Urethroplasty
Urethrotomy
Voiding symptoms

Abstract

Background: Urethral stricture affects 0.9% of men. Initial treatment is urethrotomy. Approximately, half of the strictures recur within 4 yr. Options for further treatment are repeat urethrotomy or open urethroplasty.
Objective: To compare the effectiveness and cost effectiveness of urethrotomy with open urethroplasty in adult men with recurrent bulbar urethral stricture.
Design, setting, and participants: This was an open label, two-arm, patient-randomised controlled trial. UK National Health Service hospitals were recruited and 222 men were randomised to receive urethroplasty or urethrotomy.
Intervention: Urethrotomy is a minimally invasive technique whereby the narrowed area is progressively widened by cutting the scar tissue with a steel blade mounted on a urethroscope. Urethroplasty is a more invasive surgery to reconstruct the narrowed area.
Outcome measurements and statistical analysis: The primary outcome was the profile over 24 mo of a patient-reported outcome measure, the voiding symptom score. The main clinical outcome was time until reintervention.
Results and limitations: The primary analysis included 69 (63%) and 90 (81%) of those allocated to urethroplasty and urethrotomy, respectively. The mean difference between the urethroplasty and urethrotomy groups was –0.36 (95% confidence interval [CI] –1.74 to 1.02). Fifteen men allocated to urethroplasty needed a reintervention compared with 29 allocated to urethrotomy (hazard ratio [95% CI] 0.52 [0.31–0.89]).
Conclusions: In men with recurrent bulbar urethral stricture, both urethroplasty and urethrotomy improved voiding symptoms. The benefit lasted longer for urethroplasty.

† Professor Robert Pickard died on July 24, 2018.

* Corresponding author. Institute of Health and Society, Newcastle University, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne NE2 4AA, UK. Tel. +44 191 208 5590, Fax: +44 191 208 6045.

https://doi.org/10.1016/j.eururo.2020.06.003

Patient summary: There was uncertainty about the best treatment for men with recurrent bulbar urethral stricture. We randomised men to receive one of the following two treatment options: urethrotomy and urethroplasty. At the end of the study, both treatments resulted in similar and better symptom scores. However, the urethroplasty group had fewer reinterventions.

1. Introduction

Registry studies from the USA estimate the prevalence of urethral stricture to be up to 0.9% of adult men [1]. The annular urethral scar, which commonly occurs in the bulbar segment of the urethra, results in difficulty voiding, threatening urinary retention [2]. The first occurrence of urethral stricture is usually treated by a minimally invasive technique, whereby the narrowed area is progressively widened either by cutting the scar tissue with a steel blade mounted on a urethroscope, the so-called endoscopic urethrotomy, or by the use of graduated urethral dilators. An estimated half of the men will suffer a recurrence within 4 yr requiring further intervention [3]. This can be done by an endoscopic technique or by more invasive surgery to reconstruct the narrowed area: open urethroplasty [4]. Hospital activity data suggest that repeated endoscopic urethrotomy is the most frequently used alternative [5] to treat bulbar stricture recurrence, but specialist clinical guidelines, based on cohort studies identified by a systematic review, recommend that open urethroplasty should be performed [4,6]. In this randomised trial, we aimed to clarify which procedure was best, primarily in providing symptom control but also considering duration of benefit prior to disease recurrence.

2. Patients and methods

2.1. Study design

This was an open-label patient-randomised parallel-group superiority trial recruiting across 53 National Health Service (NHS) secondary care providers in the UK (38 recruited at least one participant). The trial protocol was published, and it contains details about the methods [7].

2.2. Participants

Adult men presenting with bulbar urethral stricture disease having previously undergone at least one surgical intervention for this condition were identified. Exclusion criteria were current perineal sepsis and/or urethra-cutaneous fistula. Patients were approached and introduced to the study by clinical staff at site. Those deciding to participate completed written consent forms for the 24-mo trial period.

2.3. Randomisation and masking

Randomisation was performed using a centralised, automated application hosted by the Centre for Healthcare and Randomised Trials, University of Aberdeen, UK, and accessed by telephone or through the Internet. Participants were allocated to urethroplasty or urethrotomy in a 1:1 ratio, with recruitment site and time since last procedure ($<$12 or $\geq$12 mo) as minimisation covariates. Clinical trial unit staff were masked to allocation, but participants and surgeons could not be blinded.

2.4. Procedures

Participants were sent the trial questionnaire—which included the patient-reported outcome measure (PROM)—at baseline; preintervention; 3, 6, 9, 12, and 24 mo after the intervention; at 18 and 24 mo after randomisation; and before and after a reintervention. At the end of the study (December 2016), we sent the questionnaire to every participant in the trial. At 3, 12, and 24 mo after the intervention, research staff at site contacted participants to complete case report forms (CRFs) face to face or by telephone, with supplementation by health care record review. Clinical outcomes, including adverse events, were collected in the CRFs. Uroflowmetry was obtained at baseline, at 3 mo, and between 12 and 24 mo after surgery.

2.5. Outcomes

The primary outcome was the profile of the urinary voiding symptom score component of the surgery PROM over 24 mo following randomisation. The questionnaire has been validated in this patient group [8]. We used the area under the curve to summarise each participants' profile. The PROM has six questions about delay before starting to urinate, poor strength of urinary stream, having to strain before urinating, intermittent urinary stream, feeling of incomplete bladder emptying, and postmicturition dribbling. Each item was scored from 0 (no symptoms) to 4 (symptoms all the time), giving a total score range of 0–24. The PROM was chosen as OPEN's primary outcome to ensure a patient-centred trial that can inform patient-centred health care delivery; symptoms are likely to be the central concern for patients with bulbar urethral strictures and the reason why they look for treatment.

Patient-reported secondary outcomes were the following: a pictorial description of urine stream strength (scored from 1 [strong stream] to 4 [weak stream]), impact of urinary symptoms on daily activity (scored from 0 [not at all] to 3 [a lot]), overall satisfaction with sexual function (scored from 1 [very dissatisfied] to 5 [very satisfied]), and health-related quality of life using the EQ-5D-5 L questionnaire reported elsewhere [9].

Secondary clinical outcomes included difference in reintervention, rate of improvement of urinary flow rate, and any recurrence. We defined a reintervention for bulbar urethral stricture as any intervention subsequent to the allocated trial procedure (excluding self-dilatation). Maximum urinary flow rate (Q_{max}) was measured by asking each participant to void at least 150 ml of urine into a commercial, calibrated uroflowmeter available at their treating centre. An increase in Q_{max} of $\geq$ 10 ml/s compared with baseline was considered as an improvement [10]. Recurrence of bulbar stricture occurred if at least one of the following conditions were met during the 24 mo after randomisation: a reintervention had occurred or was scheduled, and the maximum flow rate had deteriorated to the preintervention value or the voiding score had deteriorated to baseline value.

2.6. Sample size

Sample size details were provided in the trial's published protocol [7]. Three parameters informed a revised sample size calculation (after poor recruitment was observed): the minimum clinically important difference defined as a $>$10% difference in effect estimate in the PROM

profile, power to detect any difference set at 90%, and the standard deviation (SD) of the primary outcome measure. This was calculated from the 220 measurements of postintervention PROM voiding score, scaled from 0 to 1, submitted by the first 69 participants. The observed SD was 0.15, which was increased to 0.21 to allow for subsequent changes over trial duration. This gave a revised sample size of 170 men; we aimed to recruit 210 in total to allow for 19% attrition. The trial was also powered to determine whether the use of urethroplasty would result in a 30% reduction in reintervention at 24 mo relative to urethrotomy. To detect this difference with 90% power, 104 men were required. Statistical significance was defined at the two-sided 5% level with corresponding 95% confidence intervals (CI) derived.

2.7. Statistical analysis

The statistical analysis plans are available at https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/statistical-analysis-plans-611.php. The PROM profile, calculated by summing its six questions and using all available measurements (starting at baseline that was measured immediately prior to randomisation) to construct the area under the curve using the trapezoid rule, was analysed using linear regression adjusted for minimisation covariates.

The primary analysis included all participants who had any surgery and completed at least three voiding scores: one baseline measure, one early measure (up to 12 mo after intervention), and one later measure (18 or 24 mo after randomisation). The participants were analysed as randomised, that is, they were analysed according to their allocated group regardless of the intervention received.Given the pragmatic nature of the trial, we planned sensitivity analysis to account for missing data and noncompliance. We performed a full intention-to-treat analysis using multiple imputation to include all randomised participants in the model according to their allocated intervention. We carried out a modified intention-to-treat analysis using multiple imputation to include only those participants who had surgery in the model. Both used the same imputation strategy. We explored differences between responders and nonresponders to inform our missing data model. The auxiliary variables included in the multiple imputation model were either known predictors of the outcome (ie, minimisation variables) or predictors found by calculating their correlation with the outcome in the OPEN dataset (ie, with a correlation coefficient of >0.3). We calculated an area under the curve for each imputation and combined these using Rubin's rules under a missing at random assumption [11,12]. We also explored, using pattern mixture models [11], imputation of a range of values estimated from observed data using different missing not at random scenarios. For these scenarios, we assumed that participants with missing data in the urethroplasty arm had a score from 0 to 10 units lower than the observed values; we then tested the same for those in the urethrotomy arm. We used Stata's command *rctmiss* to implement this. We performed a per-protocol analysis including participants who got the intervention they were allocated to (ie, received the treatment as randomised).

Secondary outcomes were analysed using generalised linear models appropriate for the distribution of the outcome with adjustment for minimisation and baseline variables as appropriate. We analysed time to reintervention using Cox regression (adjusting for minimisation variables and centre). For this outcome, we used the complete observation time available until database closure (at least 24 mo and up to 48 mo for some participants). We also analysed multiple reinterventions using the Andersen-Gill model. Time to recurrence was analysed using Cox regression adjusting for minimisation variables and centre.

Subgroup analyses explored the possible modification of treatment effect by including a treatment-by-factor interaction in models. Factors were time since last procedure (<12 or ≥ 12 mo) as a global measure of stricture severity, age (≤ 50 or >50 yr), stricture length (≤ 2 or >2 cm), and number of previous interventions (one or more than one). Adverse events and serious adverse events (SAEs) are presented by intervention received.

Analyses were carried out using Stata 14 (StataCorp LP, College Station, TX, USA). This study was overseen by independent trial steering and data monitoring committees.

3. Results

A total of 222 out of 1262 men identified by study sites were randomised between February 27, 2013 and December 23, 2015 (Fig. 1 and Supplementary Table 1). There were two postrandomisation exclusions because further assessment

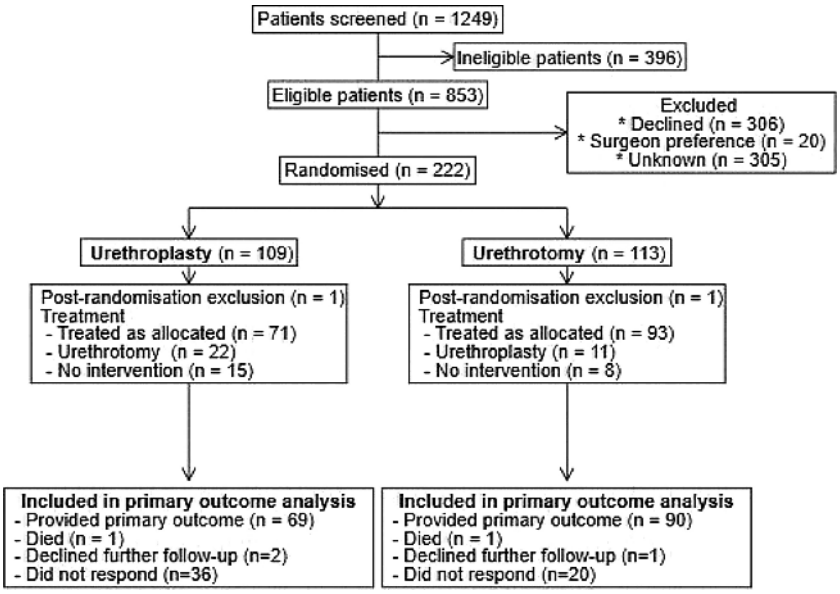


Fig. 1 – CONSORT diagram showing progress of participants through the study.

prior to intervention showed these to have been ineligible. Recorded patient characteristics were balanced at baseline, including important clinical characteristics such as length of stricture and number of previous interventions such as previous urethrotomies (Table 1). Table 2 presents the results for the primary and secondary clinical outcomes. In the primary as-randomised analysis, we included 69/108 allocated to the urethroplasty group (63% of those randomised) and 90/112 allocated to the urethrotomy group (81% of those randomised). Of the 39 participants excluded from the urethroplasty group and the 22 excluded from the urethrotomy group, 15 and eight, respectively, had no surgery at all (Supplementary Table 2). Supplementary Table 3 presents baseline characteristics by randomised arm and inclusion or exclusion from the primary analysis status. Participants were similar in most characteristics, although the proportion of participants never using intermittent self-dilatation at baseline was higher for those who provided the primary outcome than for those who did not but balanced across groups. Participants allocated to the urethrotomy arm and excluded from the analysis had a higher PROM score at baseline than those included in the analysis.

3.1. Primary outcome

The PROM profile mean (SD) over 24 mo after randomisation on a scale from 0 (no symptoms) to 24 (worst symptoms) was 7.4 (3.8) in the urethroplasty group and 7.8 (4.2) in the urethrotomy group, with a mean (95% CI) difference of −0.36 (−1.74 to 1.02; $p = 0.6$). Sensitivity analysis using multiple imputation (intention-to-treat analysis) resulted in a mean difference of −0.33 (95% CI −1.74 to 1.09; $p = 0.6$); the modified intention-to-treat analysis generated a mean difference of −0.52 (95% CI −2.0 to 0.96; $p = 0.5$). The estimate of the primary outcome was robust to sensitivity analyses using pattern mixture models for missing data for all but unrealistic, extreme scenarios (Supplemental Fig. 1). There was no evidence of treatment effect heterogeneity by subgroup (Fig. 2).

3.2. Secondary patient-reported outcomes

The impact of urinary symptom profile mean (SD) over 24 mo for the impact of urinary symptoms was 1.1 (0.8) in the urethroplasty group versus 1.0 (0.7) in the urethrotomy

Table 1 – Participant clinical characteristics and reported symptoms at baseline.

Variable	Urethroplasty (*N* = 108)	Urethrotomy (*N* = 112)
Age (yr)	49.4 (14.3); 108	48.5 (15.4); 112
Length of stricture (cm)	2.0 (1.4); 67	1.7 (1.1); 63
Duration of disease (yr)	7.3 (9.7); 78	9.9 (11.7); 80
Previous interventions (any type)	1.9 (2.0); 108	1.8 (1.7); 112
Previous dilatation	0.4 (0.8); 80	0.5 (1.8); 83
Previous urethroplasty	0.1 (0.4); 76	0.1 (0.3); 82
Previous urethrotomy	1.6 (1.8); 106	1.4 (1.0); 109
Time since last intervention (mo)		
<12	36 (33.3)	36 (32.1)
≥12	72 (66.7)	76 (67.9)
Predominant site of stricture in bulbar urethra		
Proximal	30 (27.8)	24 (21.4)
Mid	34 (31.5)	41 (36.6)
Distal	17 (15.7)	17 (15.2)
Unknown	6 (5.6)	14 (12.5)
Missing	21 (19.4)	16 (14.3)
Cause of stricture		
Unknown	76 (70.4)	81 (72.3)
Trauma	11 (10.2)	11 (9.8)
Infection	5 (4.6)	6 (5.4)
Other	12 (11.1)	7 (6.3)
Missing	4 (3.7)	7 (6.3)
Use of intermittent self-dilatation		
Never	60 (55.6)	66 (58.9)
Previously	25 (23.1)	31 (27.7)
Currently	23 (21.3)	14 (12.5)
Missing	0 (0)	1 (0.9)
Maximum urinary flow rate (ml/s)	10.0 (6.0); 83	9.7 (5.2); 90
Urethrogram performed	70 (64.8)	62 (55.4)
Urethroscopy performed	34 (31.5)	42 (37.5)
PROM		
Total voiding score mean (SD), 0 (no symptoms) to 24 (symptoms all the time)	13.5 (4.5); 104	13.2 (4.7); 109
Impact of urinary symptoms on daily activities, 0 (none) to 3 (a lot)	2.0 (1.0–3.0); 107	2.0 (1.0–3.0); 110
Satisfaction with sexual function, 1 (very satisfied) to 5 (very dissatisfied)	3.0 (2.0–4.0); 97	3.0 (2.0–4.0); 100

PROM = patient-reported outcome measure; SD = standard deviation.
Data are presented as mean (SD), count or median (p25–p75), and count for continuous variables. Binary and categorical data are presented as frequency (% out of randomised).

Table 2 – Clinical and patient-reported outcomes (mean [SD], count or % [*n*/*N*] or *n* as appropriate)[a].

Analysis	Urethroplasty (n = 108)	Urethrotomy (112)	Effect size (95% CI)	p-value
Patient-reported outcomes				
			Mean difference	
Profile void score	7.4 (3.8), 69	7.8 (4.2), 90	−0.36 (−1.74 to 1.02)	0.6
Profile impact of urinary symptoms	1.1 (0.8), 69	1.0 (0.7), 90	0.06 (−0.19 to 0.30)	0.6
Profile satisfaction with sexual function	2.9 (1.2), 63	2.5 (1.2), 87	0.35 (−0.06 to 0.75)	0.090
Clinical outcomes				
			Odds ratio	
Q_{max} improved at 12 or 24 mo from baseline[b]	19% (18/93)	13% (13/104)	2.64 (1.14–6.15)	0.024
			Hazard ratio	
Any recurrence	19	39	0.46 (0.29–0.72)	0.001
Re-intervention	15	29	0.52 (0.31–0.89)	0.017

Q_{max} = maximum urinary flow rate; SD = standard deviation.
[a] The effect sizes presented differ by outcome and are all adjusted to minimisation variables; all effect sizes are urethroplasty versus urethrotomy.
[b] Improvement defined as an increase in the flow rate of 10 ml/s or more.

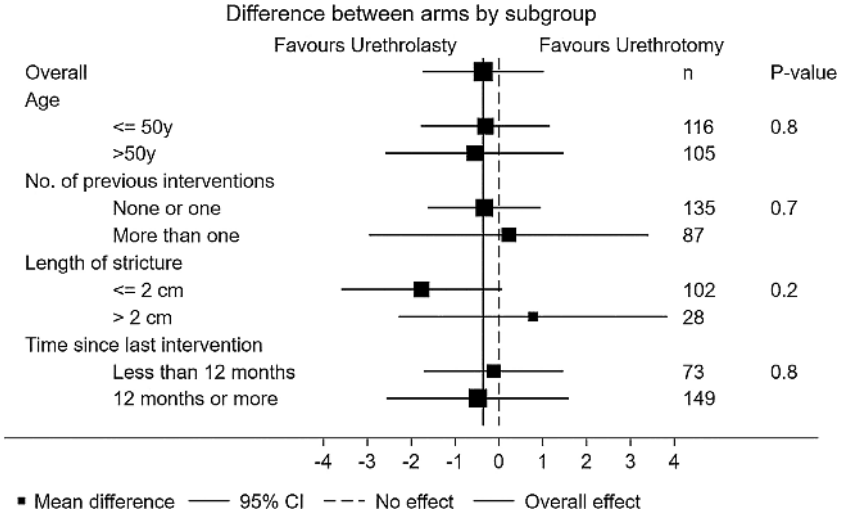


Fig. 2 – Subgroup analyses for the PROM voiding score area under the curve (calculated by including a treatment-by-factor interaction in models). CI = confidence interval; PROM = patient-reported outcome measure.

group. The adjusted mean (95% CI) difference between treatments was 0.06 (−0.19 to 0.30; $p = 0.6$). The satisfaction with sexual function profile mean (SD) over 24 mo was 2.9 (1.2) in the urethroplasty group versus 2.5 (1.2) in the urethrotomy group. The adjusted mean (95% CI) difference between treatments was 0.35 (−0.06 to 0.75; $p = 0.090$).

3.3. Reinterventions and other secondary clinical outcomes

In total, 44 participants had at least one reintervention, and there were 52 reinterventions overall. Between randomisation and end of follow-up (participants were followed up to 4 yr), 15 men in the urethroplasty group required a reintervention a median of 474 (interquartile range 399–577) d after initial surgery compared with 29 men allocated to the urethrotomy group requiring a reintervention 308 (211–448) d after surgery. The hazard ratio for time until first reintervention (95% CI) was 0.52 (0.31–0.89; $p = 0.017$), representing a 48% lower risk of reintervention with urethroplasty. Calculation including multiple reinterventions per participant gave a similar hazard ratio (95% CI) of 0.49 (0.30–0.82; $p = 0.006$). A secondary analysis involving only men who underwent the allocated intervention (per protocol) showed a hazard ratio (95% CI) for time to reintervention of 0.28 (0.15–0.55; $p < 0.001$; Fig. 3).

Participants in the urethroplasty group had twice the odds of experiencing an improvement of ≥10 ml/s in their maximum flow rate at 3 mo compared with participants in the urethrotomy group (odds ratio, ie, OR [95% CI] 2.1 [1.05, 4.12]; $p = 0.035$). At 12 or 24 mo, the 44 participants in the urethroplasty group had 2.6 times greater odds of experiencing an improvement of ≥10 ml/s in their maximum flow rate than the 63 participants in the urethrotomy group (OR [95% CI] 2.6 [1.1–6.1]; $p = 0.024$).

At the end of follow-up, there were 19 recurrences in the urethroplasty group and 39 in the urethrotomy group (hazard ratio [95% CI] 0.46 [0.29–0.72]; $p = 0.001$).

3.4. Adverse events

A total of 88 adverse events were reported during the trial, with 80 participants suffering at least one adverse event.

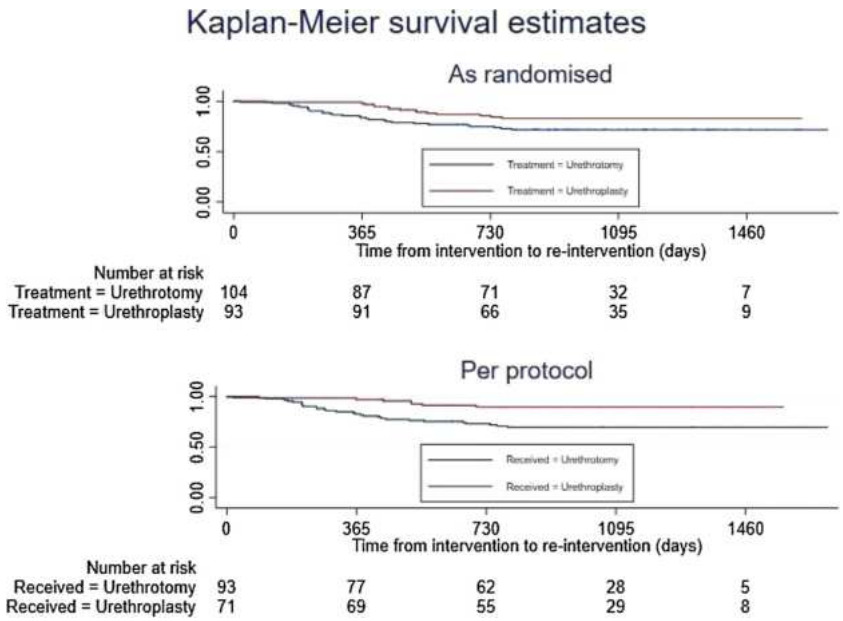


Fig. 3 – Hazard curves for reintervention by the randomised or the treatment-received group up to 4 yr after initial intervention. Analysis of participants who had surgery according to their randomised allocation (as randomised) or men who underwent the procedure allocated at randomisation (per protocol).

Out of them, 43 versus 30 suffered one event, six versus zero suffered two events, and one versus zero suffered three events in the group receiving urethroplasty versus the group receiving urethrotomy (treatment received) during the trial. See Table 3 for more information. A total of 22 SAEs were reported during the trial, with two related to the trial intervention. During the trial, 17 participants were reported to have experienced at least one SAE (seven vs 10 in the group that received urethroplasty vs the group that received urethrotomy): 14 participants suffered one SAE (six vs eight), one participant had two adverse events (zero vs one), and two participants had three adverse events (one vs one; Table 4).

4. Discussion

The OPEN trial is the first multicentre randomised controlled trial comparing the effectiveness and cost effectiveness (not reported in this paper) of the two choices available for men suffering from the recurrence of bulbar urethral stricture: endoscopic urethrotomy versus urethroplasty. We found that at 24 mo, participants in both groups had similarly improved symptom scores compared with baseline. Clinical outcomes, including time to reintervention, and urinary flow rate (the most frequently used clinical outcome [10]) favoured urethroplasty on average. These results were homogeneous across different subgroups.

The OPEN trial design followed best practice for surgical trials in a pragmatic setting: participants and clinicians could not be blinded, but central trial staff entering and analysing results were masked where possible. The use of a remote computerised randomisation system ensured allocation concealment. We set the trial in the UK NHS, recruiting from both specialist and general units. The trial's primary outcome focused on patients' symptoms since men with recurrent stricture are most concerned about their poor and prolonged voiding that threatens urinary retention, a problem that they find distressing and that negatively impacts their lives [13]. A further strength of the study is that both randomised groups were evenly balanced with respect to stricture length, aetiology, number of prior recurrences, and their prior experience of self-dilatation. The outcomes from both arms ought to be representative of a "typical" patient with a recurrent bulbar stricture with similar values to cohorts of men undergoing urethroplasty or urethrotomy in recently published studies.

We faced difficulties in recruiting and retaining participants. This could be due to several reasons. The two treatments are very different in complexity and short-term patient experience; participants will have had treatment failure to enter the trial. Furthermore, we embedded qualitative work and made changes to the design as a result of that [14]. To help improve retention, we provided different communication options, including the option to complete outcome questionnaires online (used by 30% of participants). We used automated alerts to monitor and chase overdue outcome data from participants and sites. Despite these efforts, we could include only 159/220 (72%) participants in the primary analysis: 69 (63%) allocated to urethroplasty and 90 (81%) to urethrotomy. This is a common experience in studies of urethroplasty, with the number of patients attending clinics declining with time. The reasons for the differential drop-out between randomised arms are unknown; however, these could be related to more participants receiving their allocated treatment in the urethrotomy arm or the shorter waiting time for that

Table 3 – Frequency of adverse events by treatment received.

	Urethroplasty (n = 82)	Urethrotomy (n = 115)
No. of adverse events		
0	32 (39.0)	85 (73.9)
1	43 (52.4)	30 (26.1)
2	6 (7.3)	0 (0)
3	1 (1.2)	0 (0)
Adverse events during the perioperative period		
Mouth pain	12 (14.6)[a]	2 (1.7)
Wound infection	4 (4.9)	0 (0)
Bladder "spasm" requiring treatment	2 (2.4)	1 (0.9)
Urinary infection	3 (3.7)	0 (0)
Initial failed trial without catheter	0 (0)	1 (0.9)
Adverse events during the reintervention perioperative period		
Mouth pain	0 (0)	2 (1.7)
Wound infection	0 (0)	1 (0.9)
Urinary infection	0 (0)	2 (1.7)
Urinary retention	0 (0)	1 (0.9)
Constipation	0 (0)	1 (0.9)
Adverse events during follow-up		
Erectile dysfunction	4 (4.9)	3 (2.6)
Mouth pain	4 (4.9)	0 (0)
UTI	5 (6.1)	6 (5.2)
Urinary symptom outcome	7 (8.5)[b]	6 (5.2)
Wound infection	1 (1.2)	1 (0.9)
Wound pain	5 (6.1)	1 (0.9)
Numb testicles	2 (2.4)	0 (0)
Issues related to climax	1 (1.2)[c]	0 (0)
Other[d]	1 (1.2)	3 (2.6)
Erectile dysfunction and wound infection	1 (1.2)	0 (0)
Erectile dysfunction and wound pain	1 (1.2)	0 (0)
Wound infection, UTI, and fistula	1 (1.2)	0 (0)

UTI = urinary tract infection.
[a] Two people had two events of mouth pain.
[b] One person had two new urinary symptoms.
[c] One person had two reports of issues related to climax.
[d] Upper respiratory tract infection, swollen ankles, haematuria and dysuria, and falls.

Table 4 – Frequency of serious adverse events by treatment received.

	Urethroplasty (n = 82)	Urethrotomy (n = 115)
No. of serious adverse events		
0	75 (91.5)	105 (91.3)
1	6 (7.3)	8 (7.0)
2	0 (0)	1 (0.9)
3	1 (1.2)	1 (0.9)
Serious adverse events		
Readmission to hospital	0 (0)	2 (1.7)[a]
Diverticular perforation	0 (0)	1 (0.9)
UTI	3 (3.7)	1 (0.9)
Haematuria	1 (1.2)	1 (0.9)
New urinary symptom	1 (1.2)	1 (0.9)
Wound infection	1 (1.2)	1 (0.9)
Wound pain	1 (1.2)	0 (0)
Wound infection and fistula	1 (1.2)	0 (0)
Death	0 (0)	1 (0.9)[b]
Other[c]	1 (1.2)	3 (2.6)

UTI = urinary tract infection.
[a] One person had three readmissions to the hospital.
[b] Event unrelated to the trial intervention. Death by deep vein thrombosis and pulmonary embolism.
[c] Urethral bleeding following a urethrogram, posterior circulation cerebral infarct, left hemianopia, chest pain, and cholecystitis. Two events related to the trial intervention and expected.

intervention. Owing to this observed difference, an additional statistical analysis plan was prepared by the trial team's statistical experts not involved in the data analysis of the trial. We conducted several sensitivity analyses as a result, including multiple imputation assuming a missing at random mechanism and pattern mixture models assuming missing not at random. The OPEN trial results were robust to all but unrealistic scenarios.

The percentage of SAEs was similar in both the urethroplasty and the urethrotomy groups (10.9% vs 11.3%). Given the increased complexity of urethroplasty, a greater proportion of SAEs in that group would have been expected. However, the SAE rate for urethroplasty is similar to the 30-d complication rate recently reported in the UK national database [15]. One possible explanation is that there were a total of four readmissions following urethrotomy, typically performed as a day case, for bleeding and/or retention.

A systematic literature review including data from trial registries, which was updated just prior to trial completion, did not identify further relevant trials published or in progress to compare with our design and results. However, clinical guidance suggests that urethroplasty is a better option, but this advice has been based on low-level published evidence and expert opinion so far. Outcomes for participants of our randomised trial were similar to the data from nonrandomised cohorts of patients undergoing urethroplasty or urethrotomy in Europe and the USA. The proportion of recurrences following urethrotomy and the improvement in measured flow rate found in the urethrotomy group was also similar to those found in cohorts of recently published studies [2,16] as well as in a previous randomised controlled trial of internal urethrotomy versus dilation for male urethral stricture disease [17].

5. Conclusions

Our study will help clinicians worldwide provide more accurate information on the comparative benefit of urethroplasty and urethrotomy for their male patients with recurrent bulbar urethral stricture. Our study shows that either procedure is likely to improve symptoms from baseline without risking significant harms, and therefore both should be available. The duration of this benefit is longer with urethroplasty. Patients, informed by their clinician, will need to balance these factors in the light of their individual circumstances, values, and preferences to decide which procedure to undergo. It appears that urologists are discouraged from referring men to urethroplasty if it will mean a travelling time of longer than 45 min for the patient [18]. In order to implement urethroplasty successfully in health care systems, there is a need for robust clinical pathways that ensure specialist services with sufficient resources in terms of theatre time and ongoing specialist surgeon availability. It is likely that this

will have implications for training needs within the urology speciality.

Author contributions: Luke Vale had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pickard, Vale, MacLennan, Norrie, Cook, McColl, Watkin.
Acquisition of data: Carnell, Forbes, Currer, Wilkinson, Pickard, Watkin, MacLennan, Vale, Norrie, McColl, Whybrow, Rapley.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Goulao, Pickard.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Goulao, MacLennan, Vale, Breckons, Shen.
Obtaining funding: Pickard, Vale, MacLennan, Norrie, Cook, McColl, Watkin, Andrich, Mundy, N'Dow, Payne, Barclay.
Administrative, technical, or material support: Carnell, Forbes, Currer, Wilkinson, Pickard, Watkin, MacLennan, Vale, Norrie, McColl, Forrest.
Supervision: None.
Other: None.

Financial disclosures: Luke Vale certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Robert Pickard, Graeme MacLennan, John Norrie, Luke Vale, Tim Rapley, Elaine McColl, Daniela Andrich, and Jonathan Cook all report grants from the NHS (National Institute for Health Research [NIHR]) during the conduct of the study. John Norrie reports membership of the following NIHR boards: CPR decision-making committee, Health Technology Assessment (HTA) Commissioning Board, HTA Commissioning Sub-Board (EOI), HTA Funding Boards Policy Group, HTA General Board, HTA Post-Board funding teleconference, NIHR CTU Standing Advisory Committee, NIHR HTA and Efficacy and Mechanism Evaluation Editorial Board, and Pre-exposure Prophylaxis Impact Review Panel. Luke Vale reports membership of NIHR HTA CET panel to March 2018. Elaine McColl reports grants from the NIHR Journals Library outside the submitted work. In addition, from 2013 to 2016 Elaine McColl was an editor for the NIHR Programme Grants for Applied Research series, with a fee paid to her employing organisation. Jonathan Cook was a member of the HTA Efficient Study Designs Board during part of this study's duration. James N'Dow is a member of the HTA General Board.

Funding/Support and role of the sponsor: This work was supported by the Newcastle University Hospitals NHS Foundation Trust for Research Governance, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, and the Clinical Evaluation and Trials Board (trial registration ISRCTN: 98009168).

Acknowledgements: We thank the patients and health care professionals for their participation in qualitative interviews. We also thank Stewart Barclay, the patient and service user representative on the OPEN Trial Management Group. We acknowledge the Trial Steering Committee members: Roger Kockelburg (Chair), John Matthews, Alan McNeil, Howard Kynaston, Neil Campling. Data Monitoring Committee members: Gordon Murray (Chair), Richard Martin, and Thomas Pinkney. We thank Matthew Jackson (research fellow), Gladys McPherson (data manager), Lee Munro (trial manager), Rachel Stephenson (trial manager), Sue Tremble (trial manager), Robbie Brown (trial manager), Mark Deverill (health economist), Amy Collins (project secretary), Lavinia Miceli (project secretary), and Ann Payne (project secretary). Sarah Hill and David Mott contributed to the development and interviews of the TTO exercise, and Joanne O'Connor and Beena David contributed to the interviews of the TTO exercise. Assistance was provided by Peter Murphy and Wendy Robson when conducting TTO pilots in Freeman Hospital. All the volunteers who took part in the TTO pilots and participants in TTO interviews are acknowledged. The following sites and Principal Investigators are acknowledged for their support: Mr. Trevor Dorkin, Freeman Hospital, Newcastle; Professor Nick Watkin, St George's Hospital, London; Professor Anthony Mundy, University College London Hospitals; Mr. Paul Anderson, Russells Hall Hospital, Dudley; Mrs. Suzie Venn, Queen Alexandra Hospital, Portsmouth; Mr. Ian Eardley, St James University Hospital, Leeds; Mr. David Dickerson, Weston General Hospital; Mr. Nikesh Thiruchelvam, Addenbrooke's Hospital, Cambridge; Mr. Richard Inman and Mr. Chris Chapple, Royal Hallamshire Hospital, Sheffield; Mr. Andrew Baird, University Hospital, Aintree; Mr. Andrew Sinclair, Stepping Hill Hospital; Mr. Rajeshwar Krishnanm, Kent and Canterbury Hospital; Mr. Rowland Rees, University Hospital, Southampton; Professor James N'dow, Aberdeen Royal Infirmary; Mr. Bruce Montgomery, Frimley Park Hospital, Camberley; Mr. Michael Swinn, East Surrey Hospital; Mr. Alastair Henderson, Mr. John Donohue, Maidstone Hospital; Mrs. Suzie Venn, St Richards Hospital, Chichester; Mr. Robert Mason, Torbay Hospital; Mr. Sanjeev Madaan, Darent Valley Hospital; Mr. Mustafa Hilmy, York Hospital; Miss Vivienne Kirchin, Sunderland Royal Infirmary; Kim Davenport, Cheltenham General Hospital; John McGrath, Exeter Hospital; Tim Porter, Yeovil District Hospital; Ruaraidh MacDonagh, Amerdip Birring, Musgrove Park, Taunton; Ramachandran Ravi, Basildon; Jawad Husain, Wigan; Maj Shabbir, Guy's Hospital; Omer Baldo, Airedale Hospital; Sadhanshu Chitale, Whittington Hospital; Mary Garthwaite, James Cook University Hospital; Shalom Srirangam, Royal Blackburn Hospital; Liaqat Chowoo, Bedford Hospital; Tina Rashid, Charing Cross; Rob Skyrme; Jon Featherstone, Princess of Wales Hospital, Bridgend; and Mr. Ammar Alhasso, Edinburgh; Mr Oleg Tatarov, Cardiff. We thank the following trusts for offering PIC support: Basingstoke and Northamptonshire NHS Foundation Trust; Royal Liverpool and Broadgreen University Hospitals NHS Trust; Chelsea and Westminster NHS Foundation Trust; and Wirral University Teaching Hospitals NHS Foundation Trust.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.003.

References

[1] Anger J, Buckley J, Santucci R, Elliot S, Saigal C. Trends in stricture management among male Medicare beneficiaries: underuse of urethroplasty? Urology 2011;77:481–5.
[2] Buckley JC, Heyns C, Gilling P, Carney J. SIU/ICUD consultation on urethral strictures: dilation, internal urethrotomy, and stenting of male anterior urethral strictures. Urology 2014;83:S18–22.
[3] Pansadoro V, Emiliozzi P. Internal urethrotomy in the management of anterior urethral strictures: long-term followup. J Urol 1996;156:73–5.
[4] Chapple C, Andrich D, Atala A, Barbagli G. SIU/ICUD consultation on urethral strictures: the management of anterior urethral stricture disease using substitution urethroplasty. Urology 2014;83:S31–47.

[5] Rapp DE, Chanduri K, Infusino G, et al. Internet survey of management trends of urethral strictures. Urol Int 2008;80:287–91.
[6] Wessells H, Angermeier KW, Elliott S, et al. Male urethral stricture: American Urological Association Guideline. J Urol 2017;197:182–90.
[7] Stephenson R, Carnell S, Johnson N, Brown R, Wilkinson J, Mundy A. Open urethroplasty versus endoscopic urethrotomy – clarifying the management of men with recurrent urethral stricture (the OPEN trial): study protocol for a randomised controlled trial. Trials 2015;16:600.
[8] Jackson MJ, Sciberras J, Mangera A, et al. Defining a patient-reported outcome measure for urethral stricture surgery. Eur Urol 2011;60:60–8.
[9] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.
[10] Erickson B, Breyer B, McAninch J. Changes in uroflowmetry maximum flow rates after urethral reconstructive surgery as a means to predict for stricture recurrence. J Urol 2013;186:1934–7.
[11] White IR, Thompson SG. Allowing for missing outcome data and incomplete uptake of randomised interventions, with application to an Internet-based alcohol trial. Stat Med 2011;30:3192–3207.
[12] Bell Ml, King Mt, Fairclough Dl. Bias in area under the curve for longitudinal clinical trials with missing patient reported outcome data: summary measures versus summary statistics. SAGE Open (April–June):2014;1–12.
[13] Whybrow P, Rapley T, Pickard R, Hrisos S. How men manage bulbar urethral stricture by concealing urinary symptoms. Qual Health Res 2015;25:1435–42.
[14] Whybrow P, Pickard R, Hrisos S, Rapley T. Equipoise across the patient population: optimising recruitment to a randomised controlled trial. Trials 2017;18:1–12.
[15] Payne S, Fowler S, Mundy A. Analysis of a 7-year national online audit of the management of open reconstructive urethral surgery in men. BJU Int 2020;125:304–13.
[16] Jhanwar A, Kumar M, Sankhwar N, Prakash G. Holmium laser vs. conventional (cold knife) direct visual internal urethrotomy for short-segment bulbar urethral stricture: outcome analysis. Can Urol Assoc J 2016;10:E161–4.
[17] Steenkamp J, Heyns C, de Kock M. Internal urethrotomy versus dilation as treatment for male urethral strictures: a prospective, randomized comparison. J Urol 1997;157:98–101.
[18] Consolo MJ, Syed KK, Robison C, et al. Barriers to accessing urethroplasty. Rev Urol 2016;18:188–93.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 572–580 of this issue

Is Urethrotomy as Good as Urethroplasty in Men with Recurrent Bulbar Urethral Strictures?

Nadir I. Osman, Christopher R. Chapple *

Department of Urology, The Royal Hallamshire Hospital, Sheffield, UK

Direct-vision internal urethrotomy (DVIU) and urethral dilatation (UD) have traditionally been considered as first-line treatments for primary bulbar urethral strictures in men. A randomised clinical study demonstrated no significant difference in recurrence between the two as treatments for anterior urethral strictures, with one-third of men having had prior treatment. The recurrence rate at 12 mo was approximately 40% for strictures <2 cm, 50% for strictures of 2–4 cm, and 80% for strictures >4 cm. The recurrence rate for strictures of 2–4 cm increased to 75% at 48 mo. For each 1-cm increase in length of the stricture, the risk of recurrence increased by 1.22 [1].

In recurrent urethral strictures, repeat DVIU and UD are considered to have poor outcomes unless combined with intermittent self-dilatation (ISD). Supportive evidence for this (not considering stricture length or site) is that the recurrence rate after a second DVIU/UD for a stricture recurring by 3 mo was 50–70% at 24 mo and 60–100% at 48 mo [2]. After a third DVIU/UD, the recurrence rate at 24 mo was 100% [2]. Thus, conventional wisdom has been that after a second DVIU/UD, further minimally invasive interventions are palliative. This is reflected in the International Consultation on Urological Disease guidelines, which recommend that men with bulbar strictures that recur within 6 mo or have failed to respond to a second DVIU/UD should be offered urethroplasty [3].

In this issue of *European Urology*, Goulao et al [4] report results from the OPEN trial. This is the first multicentre randomised controlled trial comparing DVIU directly with urethroplasty in men with a recurrent bulbar stricture. The primary as-randomised analysis included 69 (63%) and 90 (81%) of those allocated to urethroplasty and DVIU, respectively. While at 24-mo follow-up, both groups had a similar improvement in the primary outcome of voiding symptom score, men undergoing DVIU were twice as likely to undergo reintervention as men undergoing urethroplasty (29 vs 15; hazard ratio 0.52, 95% confidence interval 0.31–0.89). Other secondary outcomes of time to reintervention and change in maximal flow rate favoured urethroplasty on average, with similar results homogeneous across different subgroups [4]. This pragmatic study is an excellent attempt to establish the relative efficacy of DVIU and urethroplasty in real clinical practice.

Several aspects of the study design are worthy of discussion. Recruitment was problematic, with only 222 out of 853 eligible patients randomised. Of those not randomised, 306 declined, attributable to a preference for urethroplasty in 60% (Supplementary Table 1 [4]). This is understandable given that many patients who have had a failed prior intervention would be reluctant to be included in a study that has a 50% chance of randomisation to the same intervention. Indeed, the majority of patients had undergone more than one prior DVIU, with a median number (standard deviation) of 1.8 (1.7) and 1.9 (2.0) for the DVIU and urethroplasty groups, respectively. It is not clear whether those declining to take part had more difficult strictures. Retaining patients was also challenging, such that overall only 72% could be included in the primary analysis, with 81% and 63% in the urethrotomy and urethroplasty groups, respectively. The authors have attempted to address this issue in the statistical analysis.

DVIU is a routine and commonly performed procedure, in contrast to urethroplasty. Although a volume-outcome relationship is yet to be described for urethroplasty, surgeon experience and cases performed per centre are likely to be important factors. These data are not presented. The type of

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.003.
* Corresponding author. Department of Urology, The Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK.
E-mail address: c.r.chapple@shef.ac.uk (C.R. Chapple).

https://doi.org/10.1016/j.eururo.2020.07.028

procedure performed is also relevant, as it is recognised that recurrence is higher for augmentation compared to anastomotic urethroplasty. In the urethroplasty arm, 16.6% and 48.5% of procedures were anastomotic and augmentation, respectively (Supplementary Table 2 [4]). A further factor that may influence outcome is stricture length, which was relatively short in both groups (DVIU 1.7 cm, urethroplasty 2.0 cm) but not significantly different. Bulbar stricture lengths reported in the literature are in general longer [5], so shorter stricture length may have biased DVIU in comparisons of efficacy.

Most postoperative complications of urethroplasty are infection-related. A low postoperative infection rate of 8.6% was reported for the urethroplasty group (wound infection 4.9%, urinary infection 3.7%). This is similar to contemporary real-world data from the British Association of Urological Surgeons audit of 957 bulbar urethroplasties (40 surgeons, 35 centres), for which the 30-d complication rate was 5.9% [6]. At face value this suggests that the case mix in the study is representative of real clinical practice and that surgeon experience and volume were not skewed towards highly specialised surgeons operating in high-volume centres.

How best to assess outcomes has been a point of much discussion in urethral surgery. Most clinical series have focused on the "need for further intervention" to define success or failure and have ignored symptoms. The authors should be commended for focusing on patients' symptoms in the primary outcome and using a validated patient-reported outcome measure [7]. Nevertheless, it is inevitable that surgeons will be drawn to "harder" measures such as re-intervention rates or anatomic recurrence as the metrics most helpful to informing their clinical practice.

Although the study did not report anatomic recurrence, it did report reintervention. In the per-protocol analysis, 15/71 (21.1%) men had a reintervention after urethroplasty compared to 29/93 (31.2%) after DVIU. In the as-randomised analysis, 15/93 (16.1%) men post urethroplasty had a reintervention compared to 29/104 (27.9%) after DVIU. At face value, this challenges some of the long-standing assumptions held about how much better urethroplasty is than DVIU/UD for recurrent bulbar stricture.

It is important to discuss what constitutes a reintervention as there is some inconsistency in the literature. Some consider it as a further urethroplasty, while others set the bar lower at a further DVIU/UD. Still others, including us, are stricter considering the need to perform ISD as reintervention. We hold this view, as for many of our patients avoiding the need to perform lifelong ISD is one of the main reasons they choose urethroplasty over repeat DVIU/UD. Thus, we consider it to be an outcome important to patients. The study definition of further intervention did not include ISD and it is not clear what proportion of patients needed to perform long-term ISD in each group. We can see that no patients randomised to and receiving urethroplasty commenced a regimen of ISD; the data for those randomised to and receiving DVIU are not provided (Supplementary Table 2 [4]).

It is well recognised that the most accurate means of follow-up for patients after stricture surgery is direct visualisation using endoscopy or urethrography [8]. Both symptomatic improvement and flow rate can be misleading in terms of whether a stricture has recurred, as the flow rate with a normally functioning bladder does not diminish until the calibre of the urethra falls below 11Fr [9]. The absence of an anatomic outcome is a potential criticism of the study but is reflective of the pragmatism in the design and the emphasis on patient-reported measures.

The OPEN trial is the first study to provide high-quality evidence to support the recommendation that urethroplasty is the most effective treatment for recurrent bulbar strictures in contemporary practice. Despite the limitations, the authors should be congratulated on constructing and executing such an ambitious study. In particular, we would like to pay tribute to the late Professor Robert Pickard for his major contributions to this study and the advancement of evidence-based reconstructive urology.

Conflicts of interest: Neither of the authors has any relevant conflicts of interest to disclose apart from the fact that they agreed to participate in the OPEN study, but all patients declined participation as they had all had a prior intervention and were not prepared to undergo a further DVIU.

References

[1] Steenkamp JW, Heyns CF, de Kock ML. Internal urethrotomy versus dilation as treatment for male urethral strictures: a prospective, randomized comparison. J Urol 1997;157:98–101.
[2] Heyns CF, Steenhamp JW, de Kock ML, Whitaker P. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998;160:356–8.
[3] Chapple C, Andrich D, Atala A, et al. SIU/ICUD consultation on urethral strictures: the management of anterior urethral stricture disease using substitution urethroplasty. Urology 2014;83(3 Suppl): S31–47.
[4] Goulao B, Carnell S, Shen J, et al. Surgical treatment for recurrent bulbar urethral stricture: a randomised open-label superiority trial of open urethroplasty versus endoscopic urethrotomy (the OPEN trial). Eur Urol 2020;78:572–80.
[5] Palminteri E, Berdondini E, Verze P, De Nunzio C, Vitarelli A, Carmignani L. Contemporary urethral stricture characteristics in the developed world. Urology 2013;81:191.
[6] British Association of Urological Surgeons. Urethroplasty outcomes data. Summary & timescale of the data. www.baus.org.uk/patients/surgical_outcomes/urethroplasty/timescales.aspx.
[7] Jackson MJ, Sciberras J, Mangera A, et al. Defining a patient-reported outcome measure for urethral stricture surgery. Eur Urol 2011;60:60–8.
[8] Goonesinghe SK, Hillary CJ, Nicholson TR, Osman NI, Chapple CR. Flexible cystourethroscopy in the follow-up of posturethroplasty patients and characterisation of recurrences. Eur Urol 2015;68:523–9.
[9] Smith JC. Urethral resistance to micturition. Br J Urol 1968;40:125–56.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Surgery in Motion

Contemporary Techniques of Prostate Dissection for Robot-assisted Prostatectomy

Alberto Martini [a,*], *Ugo Giovanni Falagario* [b], *Arnauld Villers* [c], *Paolo Dell'Oglio* [d], *Elio Mazzone* [e], *Riccardo Autorino* [f], *Marcio Covas Moschovas* [g], *Maurizio Buscarini* [h], *Carlo Andrea Bravi* [a], *Alberto Briganti* [a], *Guilherme Sawczyn* [i], *Jihad Kaouk* [i], *Mani Menon* [j], *Silvia Secco* [d], *Aldo Massimo Bocciardi* [d], *Gongxian Wang* [k], *Xiaochen Zhou* [k], *Francesco Porpiglia* [l], *Alexandre Mottrie* [e], *Vipul Patel* [g], *Ashutosh K. Tewari* [m], *Francesco Montorsi* [a], *Richard Gaston* [n], *N. Peter Wiklund* [m], *Ashok K. Hemal* [o]

[a] *Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy;* [b] *Department of Urology and Organ Transplantation, University of Foggia, Foggia, Italy;* [c] *Department of Urology, CHU Lille, Université de Lille, Lille, France;* [d] *Department of Urology, Niguarda Hospital, Milan, Italy;* [e] *Department of Urology, Onze Lieve Vrouw Hospital, Aalst, Belgium;* [f] *Department of Urology, Department of Surgery, Virginia Commonwealth University Health System, Richmond, VA, USA;* [g] *AdventHealth Global Robotics Institute, Celebration, FL, USA;* [h] *Università Campus Biomedico, Rome, Italy;* [i] *Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, OH, USA;* [j] *Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA;* [k] *Department of Urology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China;* [l] *Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy;* [m] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [n] *Department of Urology, Clinique Saint Augustin, Bordeaux, France;* [o] *Department of Urology, Wake Forest School of Medicine, Winston-Salem, NC, USA*

Article info

Article history:
Accepted July 16, 2020

Associate Editor:
Alexandre Mottrie

Keywords:
Prostate cancer
Prostatectomy
Robotics
Surgery
Technique

Please visit www.europeanurology.com and www.urosource.com to view the accompanying video.

Abstract

Background: Over the years, several techniques for performing robot-assisted prostatectomy have been implemented in an effort to achieve optimal oncological and functional outcomes.
Objective: To provide an evidence-based description and video-based illustration of currently available dissection techniques for robotic prostatectomy.
Design, setting, and participants: A literature search was performed to retrieve articles describing different surgical approaches and techniques for robot-assisted radical prostatectomy (RARP) and to analyze data supporting their use. Video material was provided by experts in the field to illustrate these approaches and techniques.
Surgical procedure: Multiple surgical approaches are available: extraperitoneal, transvesical, transperitoneal posterior, transperitoneal anterior, Retzius sparing, and transperineal. Surgical techniques for prostatic dissection *sensu strictu* are the following: omission of the endopelvic fascia dissection, bladder neck preservation, incremental nerve sparing by means of an antegrade or retrograde approach, and preservation of the puboprostatic ligaments and dorsal venous complex. Recently, techniques for partial prostatectomy, as either anterior or Menon precision prostatectomy, have been described.
Measurements: Different surgical approaches and techniques for RARP have been analyzed.

* Corresponding author.Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Via Olgettina, Milan, 60-20132, Italy.
E-mail addresses: martini.alberto@hsr.it, a.martini.md@gmail.com (A. Martini).

https://doi.org/10.1016/j.eururo.2020.07.017

Results and limitations: Two randomized controlled trials evaluating the extraperitoneal versus the transperitoneal approach have demonstrated similar results. Level I evidence on the Retzius-sparing approach demonstrated earlier return to continence than the traditional anterior approach. The question whether Retzius-sparing RARP is associated with a higher rate of positive surgical margins is still open due to the intrinsic bias in terms of surgical expertise in the available comparative studies. This technique also offers an advantage in patients who have received kidney transplantation. Retrospective evidence seems to suggest that the more the anatomical dissection (eg., more periprostatic tissue is preserved), the better the functional outcome in terms of continence, but two randomized controlled trials evaluating the different techniques of dissection have so far been produced. Partial prostatectomies should not be offered outside clinical trials.
Conclusions: Several techniques and approaches are available for prostate dissection during RARP. While the Retzius-sparing approach seems to provide earlier return to continence than the traditional anterior transperitoneal approach, no technique has been proved to be superior to other(s) in terms of long-term outcomes.
Patient summary: We have summarized available approaches for the surgical treatment of prostate cancer. Specifically, we described the different techniques that can be adopted for the surgical removal of the prostate using robotic technology.

1. Introduction

Anatomical studies performed during the 1970s and early 1980s have set the foundations to the current knowledge of the periprostatic anatomy [1,2]. Since then, several major and minor modifications have been proposed in an effort to respect the periprostatic anatomy as much as possible during the dissection phase of radical prostatectomy (RP) [3–19].

Almost 3 decades after the studies that changed the RP field, the introduction of robots led us to achieve a further level of precision during surgery. In fact, thanks to the magnification and the millimetric robotic instruments, more detailed understanding of the periprostatic anatomy has been achieved [20,21]. This ultimately translated into a more anatomical approach and a higher level of tissue preservation during prostatectomy.

Although multiple techniques for robot-assisted RP (RARP) have been described over the years, the extraperitoneal and the transperitoneal approach remained the two main approaches. During the dissection phase of prostatectomy, the main implementations have been omission of the endopelvic fascia dissection, incremental nerve sparing (by means of an antegrade or a retrograde approach), and preservation of the puboprostatic ligaments [3–17]. Additionally, thanks to the implementation of multiparametric magnetic resonance imaging (mpMRI) in the diagnostic and staging prostate cancer pathways, techniques for partial prostatectomy have also been described [18–20].

Vis et al [22] have recently summarized the available evidence and techniques on posterior, anterior, and periurethral reconstruction after prostatectomy in an effort to provide with a better understanding of the pelvic floor anatomy, also allowing for better training of future generation of urologists. The aim of the present study is to focus on the dissection phase of prostatectomy, describing the surgical techniques and summarizing the current evidence supporting their implementation.

2. Patients and methods

2.1. Selection of surgical approaches

By means of a review of the literature, relevant articles on currently used surgical techniques have been identified. Articles published in English peer-reviewed literature were selected (2000 through May 2020), based on the presence of a detailed anatomical description of the technique. Each author provided his/her opinion regarding the summary of the current evidence. Video clips included in this study were provided by experts in the field.

2.2. Surgical approaches for RARP

2.2.1. Extraperitoneal

In the extraperitoneal approach, the space between the rectus abdominis and the posterior sheet of the muscle is developed by means of a dilating balloon. The ports are placed in the extraperitoneal space, and the space of Retzius is developed further. The subsequent steps follow those of the transperitoneal anterior approach [3].

2.2.2. Transvesical

The transvesical approach can be performed in an extraperitoneal fashion if the ports are placed directly inside the urinary bladder, and the procedure is initiated under pneumovesicum, or in a transperitoneal fashion, where the bladder is incised and the procedure performed transvesically [19]. After bladder neck (BN) excision (Fig. 1), the procedure is carried out similarly to the transperitoneal anterior technique [4,23].

2.2.3. Transperitoneal posterior

In the transperitoneal prostatectomy, the ports are placed in the peritoneal cavity.

The original approach for laparoscopic prostatectomy entailed a posterior retrovesical approach to the vasa

Fig. 1 – Circumferential bladder neck dissection during transvesical prostatectomy.

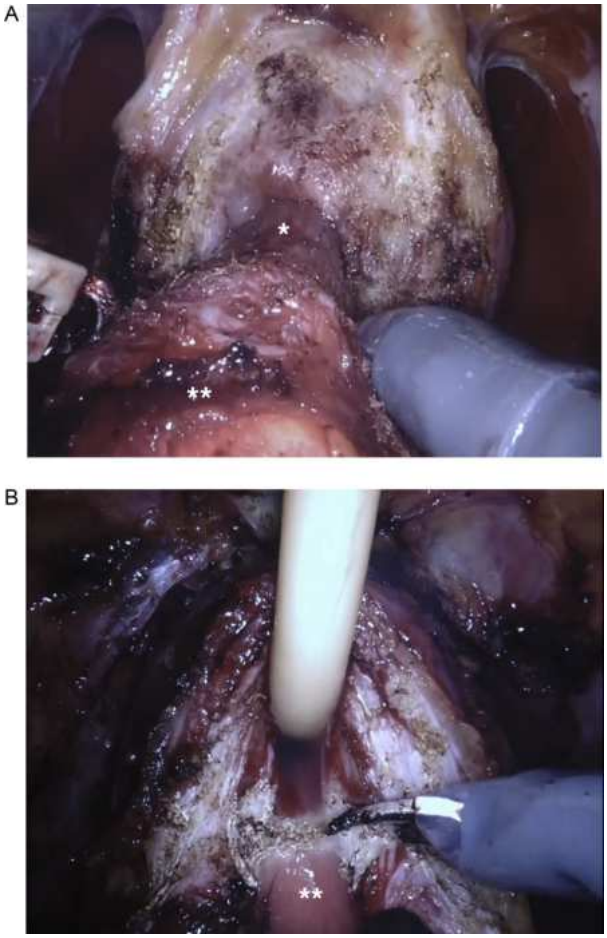


Fig. 2 – Bladder neck dissection: (A) preservation of the muscle fibers (*), (B) section of the bladder neck after a direct access into the bladder (**).

deferentia and seminal vesicles, continuing the dissection anteriorly [5]. This approach has been the cornerstone for robotic prostatectomy and still represents a widely used technique.

After the perineotomy at the lower peritoneal fold, the vasa deferentia are identified and transected, the seminal vesicles are carefully dissected free, and the prostatic base is identified. At this point, the Denonvilliers fascia is incised and the prostatic base is dissected posteriorly until the apex of the prostate is seen. After having completed these steps, the dissection moves anteriorly.

Following incision of the parietal peritoneum, the bladder is released. The space of Retzius is developed, and the fatty tissue surrounding the prostate is cleared. The BN can be either preserved or sacrificed (Fig. 2A and 2B, respectively). In the latter, the anterior wall of the bladder is incised and the BN sacrificed.

At this point, since the Denonvilliers fascia has already been incised, the prostate is dissected on its posterolateral aspects and the dissection then moves to the apex and, after having controlled the prostatic pedicles and the dorsal venous complex (DVC), the urethra is transected.

2.2.4. *Transperitoneal anterior*

This approach begins with the incision of the parietal peritoneum lateral to the lateral umbilical ligaments. The bladder is released and the space of Retzius developed. The BN is either preserved or sacrificed, and the dissection moves posteriorly. The retrotrigonal space is developed until the seminal vesicles and the vasa deferentia are identified. The vasa deferentia are transected and their distal part used for lifting the prostate (Fig. 3). This facilitates the isolation and dissection of the seminal vesicles. The Denonvilliers fascia is then incised. After this step, the procedure follows the same steps as those of the transperitoneal posterior prostatectomy [6,7].

2.2.5. *Transperitoneal lateral*

In the lateral approach, the peritoneum is incised solely lateral to the right umbilical ligament. The space is developed caudally until the pubic bone is reached. At this point, the right prostate vesical angle is identified. The dissection of the prostate begins at the right base, the right neurovascular bundle (NVB) is pushed laterally, and the right hemigland is dissected free without resecting the DVC and the detrusor apron. The prostatic dissection continues on the base through left side after careful dissection of the seminal vesicles. The dissection of the left hemigland is performed without developing the space of Retzius on the left side, allowing for the preservation of the detrusor apron, DVC, and puboprostatic ligaments (please see section 2.3.4).

2.2.6. *Transperitoneal Retzius-sparing RARP*

The preservation of the space of Retzius (or Bocciardi approach) during RARP was first described in 2010. The anatomic rationale of this technique stems from the preservation of the anterior structures involved in continence and potency preservation, such as pubovesical ligaments, puboprostatic fascia, NVBs, accessory pudendal artery, and the DVC. This approach encompasses incising the parietal peritoneum at the anterior surface of the vesicorectal pouch, at the level of the seminal vesicles (Fig. 4). After having dissected the vasa deferentia and the seminal vesicles, and retracted them by means of two sutures placed transabdominally, dissection of the prostate is carried out in an antegrade fashion. The Denonvilliers fascia is separated by the posterolateral surface of the

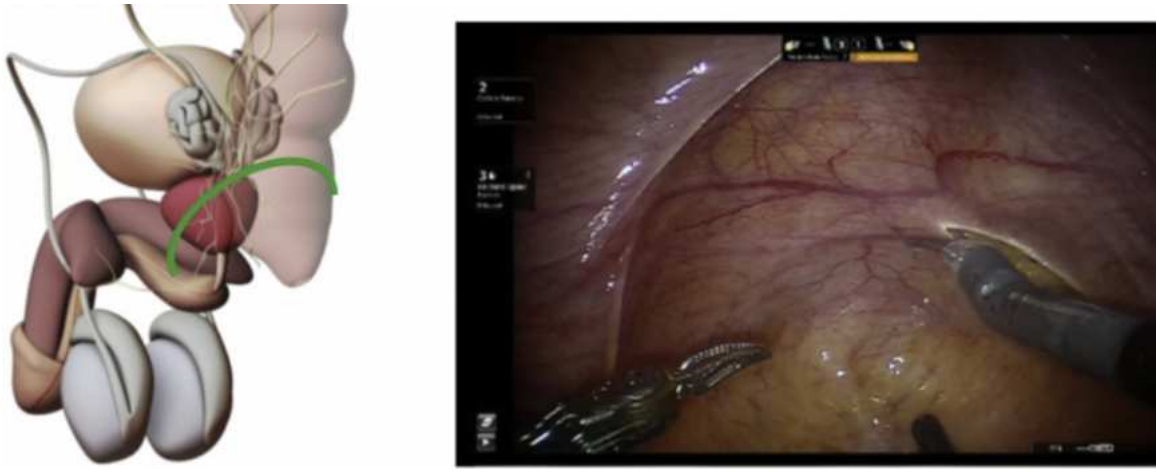


Fig. 3 – Incision of the peritoneum for the Retzius-sparing approach.

prostate, and the prostatic apex is reached. Intrafascial anterograde nerve sparing is performed when oncologically safe. Conversely, in case of more advanced disease, an interfascial or extrafascial antegrade dissection is performed. Thereafter, the surgeon goes back to identify the vesicoprostatic plane and dissect the BN. To easily identify the BN orifices during the first steps of the anastomosis, two short stitches can be placed at 6 and 12 o'clock positions. The anterior surface of the prostate is then dissected in an antegrade fashion, without incising the Santorini plexus. The section of the urethra completes the prostatic dissection [8].

2.2.7. *Transperineal*

The transperineal approach was the first approach to be described for RP in 1905 by Young [9]. Over the past few years, this technique has gained attention again, especially thanks to the introduction of the Da Vinci SP robot. Access to the prostatic fossa by means of the transperineal approach is slightly more difficult than by the transabdominal approach. After having performed a transversal incision in the perineum on a semicircumferential line connecting the ischial tuberosity, the rectourethralis muscle is divided, the external urethral sphincter is retracted, and the pubococcygeus branches of the levator ani are divided. The robot is then docked, and the prostate is identified. The Denonvilliers fascia is dissected, and the prostate is freed toward the vasa deferentia and seminal vesicles (Fig. 5A). The dissection then moves laterally and the NVBs are dissected. The apical dissection is then performed, and the anterior prostatic dissection in a caudocranial fashion finally completes the operation (Fig. 5B) [10,24].

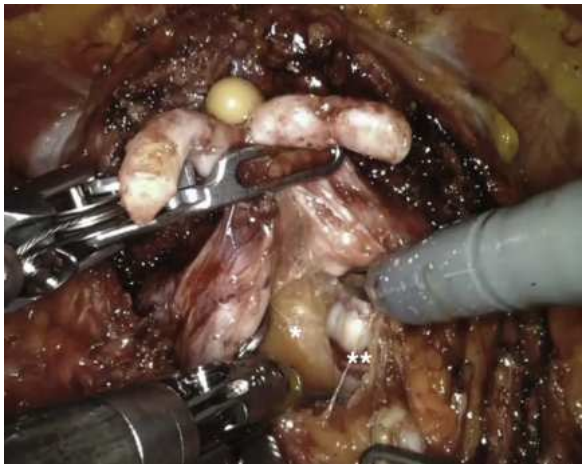


Fig. 4 – The transected vas is used to lift the prostate and seminal vesicles (SVs) during the transperitoneal anterior approach. The SVs are lifted and this movement medializes the SVs in order to facilitate their dissection. The right SV (**) is gently lateralized in order to access the medial avascular plane (*).

2.3. *Prostatic dissection sensu strictu*

2.3.1. *Endopelvic fascia*

After having released the bladder, the endopelvic fascia is generally incised and the prostate is then released anterolaterally [6]. The resulting increased prostatic mobility might help in the dissection of the NVBs, given the possibility of applying more countertraction on the prostate. The endopelvic fascia can be preserved, but this might result in lower prostatic mobility and might render the prostatic dissection more difficult in case of larger prostates [7].

2.3.2. *Bladder neck*

After having identified the prostate-vesical junction and having developed this plane, the BN can be identified in the midline and its muscle fibers can be preserved, after a gentle dissection. In case a non-BN–sparing surgery is carried out, the bladder is incised by means of cautery and the BN is circumferentially excised.

2.3.3. *Neurovascular bundles*

Two techniques are available for the dissection and NVB preservation: antegrade or retrograde [11,12].

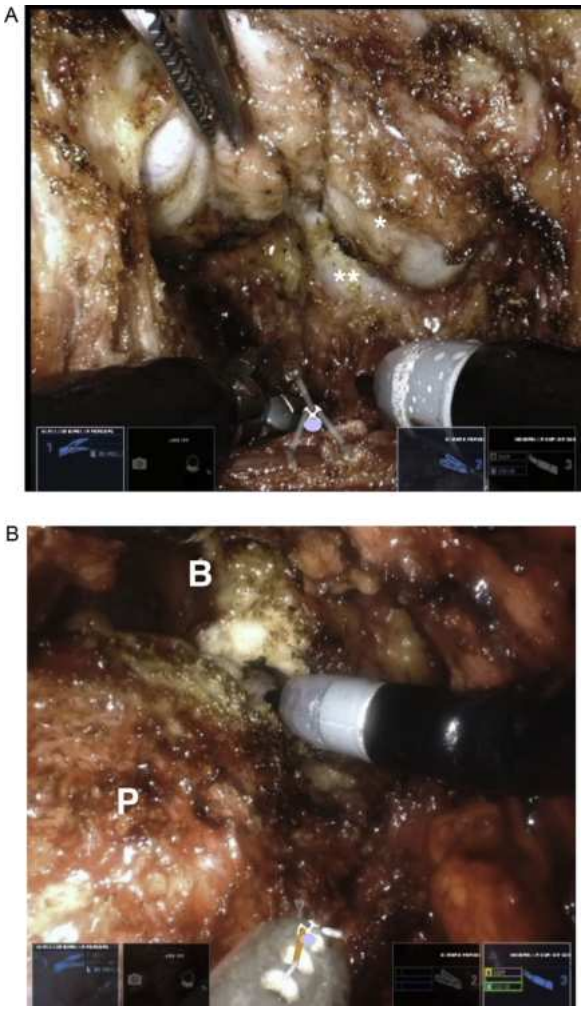


Fig. 5 – (A) Development of the posterior plate in a caudocranial fashion during the transperineal prostatectomy, and identification of the right seminal vesicle (*) and vas right deferens (**). (B) Bladder neck sectioning, in a caudocranial fashion, completes the operation. B = bladder; P = prostate.

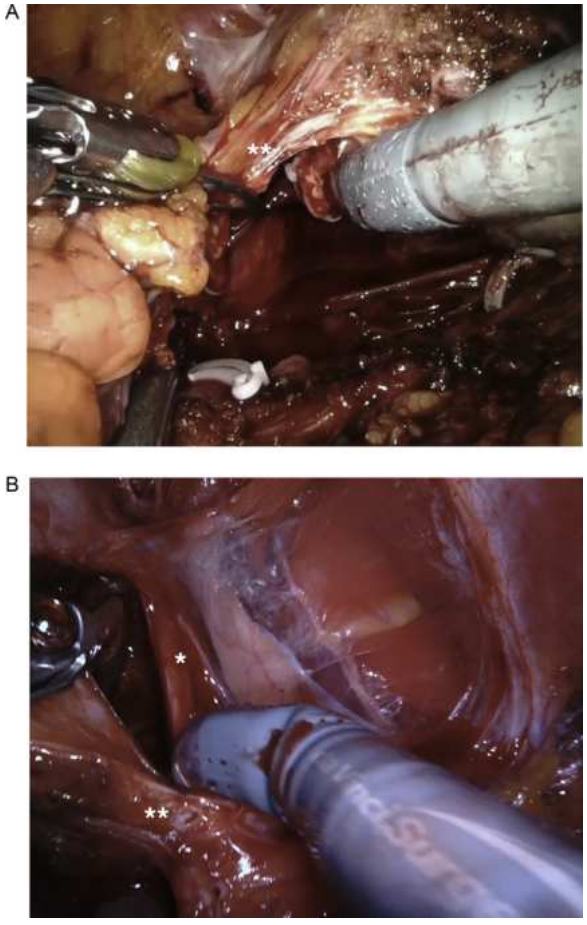


Fig. 6 – (A) Antegrade nerve sparing: the prostatic pedicle (**) is identified and dissected; the dissection continues in an antegrade fashion. (B) Retrograde nerve sparing: the neurovascular bundle (*) is identified and dissected toward the prostatic pedicle (**) in a retrograde fashion; at this point, the pedicle is sectioned.

After the seminal vesicle release and vasa deferentia transection, the prostate is lifted, and the Denonvilliers fascia is identified and incised using sharp dissection. The prostate is dissected posteriorly from the Denonvilliers fascia. The dissection then moves posterolaterally until the NVB becomes evident. After having completed this step, the subsequent one entails releasing the NVB from the posterolateral prostatic surface. During an antegrade dissection, the triangle between the pedicle and the prostatic pseudocapsule at the base is identified after gentle traction on the bundle and prostate counter traction. Once the desired plane for NS is identified, the dissection is carried out proceeding anteromedially toward the prostatic apex (Fig. 6A) [11].

The retrograde approach encompasses peeling of the lateral prostatic fascia (LPF) from the prostatic pseudocapsule. A gentle dissection of the LPF at the level of the mid-prostate is carried out in order to avoid a pseudocapsule breach. If present, one of the landmarks in this step can be the prostatic artery that can help in delineating the NVB course in a retrograde manner until the prostatic pedicle is encountered [14]. Once the desired plane is identified, the dissection proceeds caudally so that the space created during the posterior dissection is identified, and the bundle at this point is free. Dissection of the bundle proceeds toward the pedicle in a retrograde fashion (Fig. 6B). The pedicle is identified at its entry on the posterolateral angle of the base of the prostate, clipped, and dissected [13].

Regarding the degree of preservation of the NVB, this can be preserved in toto (intrafascial dissection) or partly (interfascial dissection), or dissected completely (extrafascial dissection) [25]. Tewari et al [26] have described a graded approach for NVB preservation, where grade 1 corresponds to a complete intrafascial dissection and grade 4 to an extrafascial dissection. Grades 2 correspond to an interfascial dissection that is carried out by sectioning the venous plane of the bundle in the former case and along the adipose tissue of the bundle in the latter case.

Schatloff et al [12] have also described a graded approach for NVB preservation, which consists of a five inverse-graded scale, with grade 1 corresponding to the extrafascial

dissection. They used the "landmark artery" that runs on the lateral border of the prostate as a reference point for dissection. Grade 5 corresponds to a complete intrafascial dissection, grades 4 and 3 to a dissection immediately medial and that immediately lateral to the landmark artery, respectively. Grade 2 represents a dissection lateral to the artery in the adipose tissue with embedded vessels.

2.3.4. DVC and puboprostatic ligaments

When dissecting the anterior side of the prostate, a plane can be developed between the anterior fibromuscular stroma and the detrusor apron [14]. This dissection technique allows for complete preservation of the structures lying anteriorly to the prostate, also known as the pubovesical complex [15].

2.3.5. Apical dissection

The dissection of the prostatic apex can be carried out with a sharp and direct division of the membranous urethra at the level of the urethroprostatic junction. Alternatively, it can be performed by progressively dissecting the three different muscular layers at the level of the urethral sphincter complex (rhabdosphincter, circular smooth muscle, longitudinal smooth muscle, and mucosa), as described in the "collar" technique. During this phase, rotation of the prostate helps with the dissection and delineation of the apex laterally and posteriorly [27].

2.4. Novel techniques for robot-assisted partial and total prostatectomy

2.4.1. Anterior prostatectomy

Villers et al [16,17] have described the anterior partial prostatectomy for patients with organ-confined disease, grade group $\leq$3, and a tumor in the anterior prostate. The technique entails the dissection of the BN, transition zone and anterior fibromuscular stroma along with the preservation of the posterolateral aspect of the submontanal urethra, peripheral zone, and periprostatic tissues. At the end of the dissection, the anterior part of the bladder that had initially been sectioned is sutured to the anterior urethra.

2.4.2. Menon precision prostatectomy

The Menon precision prostatectomy (MPP) technique consists in the dissection of the prostate leaving 1–2 mm of glandular tissue posterolaterally, along the course of the NVB for patients with unilateral organ-confined disease with grade group $\leq$3 and prostate-specific antigen (PSA) $\leq$15 ng/ml at the time of diagnosis [18]. All the other steps mirror those of anterior prostatectomy.

2.4.3. Robotic total prostatectomy

Robotic total prostatectomy (RTP) has recently been described for patients who meet the eligibility criteria for active surveillance and have severely enlarged glands resulting in lower urinary tract symptoms refractory to medical therapy. The RTP entails a dissection between the posterior surface of the prostate and the pseudocapsule. This allows removal of all the three prostatic zones (central, transitional, and peripheral). By avoiding dissection below the pseudocapsule, the seminal vesicles, ampulla of vasa deferentia, and NVBs are preserved completely [28].

3. Results

3.1. Surgical approach

Few randomized controlled trials (RCTs) have been produced over the years, and the vast majority of the published studies regarding surgical techniques are represented by retrospective evidence.

Two RCTs have evaluated the extraperitoneal versus the transperitoneal approach [29,30]. Both trials, even if limited by their small sample size, demonstrated similar outcomes of the two approaches, with one showing reduced time to solid diet when the extraperitoneal approach was chosen [30]. The extraperitoneal approach has the advantage of not violating the peritoneal cavity. Disadvantages include slightly longer time for port placement than the transperitoneal approach and a narrower operative space that might represent a limitation for performing extended pelvic lymph node dissection.

The only level I evidence currently available concerning the superiority of a technique over another is an RCT by Dalela et al [31] demonstrating an earlier return to continence with the Retzius-sparing RARP (RS-RARP) technique than with the anterior approach. Overall, this difference in terms of continence recovery (zero to one security pad per day) was annihilated at the 12-mo follow-up. Yet, if the definition of continence was restricted to zero pads per day, a statistically significant difference in favor of RS-RARP was still observed at the 12-mo follow-up. Noteworthy, this pivotal study had the intrinsic bias that the operating surgeon had greater experience with the anterior approach and, despite that, the RS technique emerged as the technique associated with an earlier return to continence recovery [31,32]. Another advantage of the Retzius-sparing technique is observed when performing RP in patients after kidney transplant [33].

Concerning the other techniques, no level I evidence is available demonstrating the superiority of one over another, and each technique is generally used in accordance with the surgeon's preferences.

Few studies have reported experience with a transvesical approach. Recently, Zhou et al [19] reported encouraging data in a series of 35 patients. One potential advantage of this technique is that urologists are generally well acquainted with this approach, which mirrors partial prostatectomy [4]. In addition, this has the advantage of sparing the Retzius space, and it makes it easier to deal with larger prostate with respect to the Bocciardi approach. A potential drawback of this technique could be theoretically represented by a higher chance of acute urinary retention for intravesical clot formation. Further data on this approach are needed to better evaluate its role in preservation.

The transperineal approach for RARP has recently gained attention again due to the advent of the SP Da Vinci robotic platform, and the first experience has recently been reported [10].

3.2. Techniques for prostatic dissection

No RCTs aimed at evaluating differences in the prostatic dissection itself during RARP have been produced. In a subgroup analysis of an RCT evaluating the preservation of the BN versus no preservation including patients treated with open and RARP, the preservation of the BN provided earlier return to continence [34].

Retrospective evidence seems to suggest that preservation of the endopelvic fascia, as well as the DVC and puboprostatic ligaments, might aid in earlier return to continence [15,35]. Concerning the degree of NVB preservation, there is presently no consensus on the system that should be used [20].

Concerning apical dissection, adoption of the "collar" technique seems to help in reducing apical positive surgical margins [27].

3.3. Partial prostatectomy

Both the MPP and the anterior partial prostatectomy seem to be promising procedures. Currently, none represents the standard of care, given the absence of RCTs evaluating the oncological outcomes of these procedures with respect to RP. The major drawback of the MPP is that PSA invariably persists after the procedure and a definition of "response" will have to be defined. However, an RCT is currently ongoing evaluating MPP versus RP.

3.4. Summary of evidence

Table 1 summarizes the current evidence regarding the techniques for robotic prostatectomy. Concerning RP, there is level I evidence showing earlier return to continence with the Retzius-sparing approach. This approach also offers an advantage for performing RARP in patients who have received kidney transplantation. Regarding the dissection phase of the prostatectomy, there is a lack of prospective studies evaluating the role of the techniques for dissection during prostatectomy.

Given the lack of prospective comparative evidence, partial prostatectomies should not be offered outside clinical trials.

4. Discussion

In this review, we summarized the current evidence concerning the approaches and techniques for robotic prostatectomy and briefly described the surgical techniques. Presently, there is still a lack of level I evidence in many subfields of robotic prostatectomy. In accordance with the available evidence and retrospective studies, a summary of evidence as well as authors' recommendations is provided.

Several approaches and techniques are available for performing RARP. Evidence seems to suggest that RS-RARP allows for faster continence recovery without increasing the risk of complications [31,32]. Presently, the major concern of the RS approach is the rate of positive surgical margins relative to the standard approach, especially in case of tumors that are located or have invaded the anterior fibromuscular stroma [36,37]. This difference might be related to the learning curve of RS-RARP. Indeed, all included studies relied on surgeons with extensive expertise with standard RARP and only limited experience for RS-RARP [36]. However, the largest comparative retrospective study suggested that the rate of positive surgical margins of RS-RARP versus standard RARP is comparable [38]. Despite that, the question whether RS-RARP is associated with a higher rate of positive surgical margins is still open. Future RCTs relying on surgeons with the same baseline expertise for both approaches are needed to solve this dilemma. Concerning the various techniques for the dissection of the prostate, no RCT is available, and retrospective evidence seems to suggest that the more the preservation of anatomical structures, the better the outcomes. However, studies aimed at evaluating the role of each technique in the long term are currently lacking. Additionally, there is a lack of uniformity when interpreting studies, since not all consider patients with complete dryness as continent and some of them still include patients using one pad among continent individuals.

The transvesical approach might seem to be a reasonable option to "anteriorly" spare the Retzius space, and

Table 1 – Summary of the available evidence regarding surgical approaches and techniques

	Summary of evidence	Level of evidence
Surgical approach for RARP	The Retzius-sparing approach results in earlier return to continence with respect to the anterior approach	Level I
	The Retzius-sparing approach should be performed in patients after kidney transplantation	Authors' opinion
Prostatic dissection	Retrospective evidence suggests that the more the preservation of periprostatic structures, the better the functional outcomes	Level IV
	In case of anterior tumor, the pubovesical complex should not be preserved	Authors' opinion
Partial prostatectomy	Partial prostatectomies should not be offered outside clinical trials	Authors' opinion
Total prostatectomy	Total prostatectomies should not be offered outside clinical trials	Authors' opinion

RARP = robot-assisted radical prostatectomy.

urologists are generally familiar with this technique since many steps are similar to those of the simple prostatectomy. Yet, further studies are needed to assess its effectiveness, learning curve, and outcomes in the long term.

Encouraging results have also been reported recently for the transperineal approach. This technique has the potential to further decrease hospital stay and the need for postoperative pain therapy [39]. However, transitioning from an abdominal approach to the transperineal would likely require some learning curve, and studies are needed to demonstrate the oncological safety of this approach in case of advanced disease, when a wider dissection is required.

Thanks to the advances in the mpMRI field, a partial resection of the prostate can be planned in selected candidates [16,18]. Regarding the partial prostatectomy techniques, functional outcomes are expected to be good in selected patients. Potentially, in addition to RCTs, a novel definition of PSA response after the procedure would likely be required in an effort to assess the oncological success of the procedure.

Indeed, we want to emphasize that the best technique is the one that is tailored to patient's anatomy and takes into consideration the tumor stage and grade. In a holistic approach, the best outcomes are achieved by integrating an optimal preoperative plan into an excellent dissection and reconstruction strategy or into a postoperative strategy. Interestingly, despite that different approaches and techniques might result in an earlier return to continence, differences in the functional outcomes seem to be annihilated over a long-term period. This is in keeping with Vis et al [22] who report similar continence rates at the 12-mo assessment despite different reconstruction techniques.

5. Conclusions

Herein, we provide a video-based description of contemporary approaches and dissection techniques for RARP. While evidence supporting the use of one over the others remains limited, the RS-RARP approach seems to be superior in terms of early return to continence. Partial prostatectomy should still be considered investigational. Ultimately, surgeon's preference and expertise remain the key for the adoption of one technique over the others.

Author contributions: Alberto Martini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Martini, Hemal.
Acquisition of data: None.
Analysis and interpretation of data: None.
Drafting of the manuscript: Martini, Falagario, Villers, Mazzone, Dell'Oglio, Wiklund, Autorino, Hemal.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Porpiglia, Mottrie, Patel, Tewari, Montorsi, Wiklund, Hemal.
Other: None.

Financial disclosures: Alberto Martini certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.
Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.07.017.

References

[1] Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:198–200.
[2] Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate 1983;4:473–85.
[3] Semerjian A, Pavlovich CP. Extraperitoneal robot-assisted radical prostatectomy: indications, technique and outcomes. Curr Urol Rep 2017;18:42.
[4] Gao X, Pang J, Si-Tu J, et al. Single-port transvesical laparoscopic radical prostatectomy for organ-confined prostate cancer: technique and outcomes. BJU Int 2013;112:944–52.
[5] Guillonneau B, Vallancien G. Laparoscopic radical prostatectomy: the Montsouris technique. J Urol 2000;163:1643–9.
[6] Menon M, Shrivastava A, Bhandari M, Satyanarayana R, Siva S, Agarwal PK. Vattikuti Institute prostatectomy: technical modifications in 2009. Eur Urol 2009;56:89–96.
[7] Martini A, Tewari AK. Anatomic robotic prostatectomy: current best practice. Ther Adv Urol 2019;11:1756287218813789.
[8] Galfano A, Ascione A, Grimaldi S, Petralia G, Strada E, Bocciardi AM. A new anatomic approach for robot-assisted laparoscopic prostatectomy: a feasibility study for completely intrafascial surgery. Eur Urol 2010;58:457–61.
[9] Young HH. The early diagnosis and radical cure of carcinoma of the prostate. Being a study of 40 cases and presentation of a radical operation which was carried out in four cases. J Urol 1905;2002 (168):914–21.
[10] Bertolo RG, Garisto J, Eltemamy M, Kaouk J. Pure single-site transperineal robotic radical prostatectomy: first clinical report using the SP surgical system. Eur Urol Suppl 2019;18:e2282.
[11] Martini A, Cumarasamy S, Haines III KG, Tewari AK. An updated approach to incremental nerve sparing for robot-assisted radical prostatectomy. BJU Int 2019;124:103–8.
[12] Schatloff O, Chauhan S, Sivaraman A, Kameh D, Palmer KJ, Patel VR. Anatomic grading of nerve sparing during robot-assisted radical prostatectomy. Eur Urol 2012;61:796–802.
[13] Coughlin G, Dangle PP, Palmer KJ, Samevedi S, Patel VR. Athermal early retrograde release of the neurovascular bundle during nerve-sparing robotic-assisted laparoscopic radical prostatectomy. J Robot Surg 2009;3:13–7.
[14] Myers RP. Detrusor apron, associated vascular plexus, and avascular plane: relevance to radical retropubic prostatectomy–anatomic and surgical commentary. Urology 2002;59:472–9.
[15] Asimakopoulos AD, Annino F, D'Orazio A, et al. Complete periprostatic anatomy preservation during robot-assisted laparoscopic radical prostatectomy (RALP): the new pubovesical complex-sparing technique. Eur Urol 2010;58:407–17.

[16] Villers A, Puech P, Flamand V, et al. Partial prostatectomy for anterior cancer: short-term oncologic and functional outcomes. Eur Urol 2017;72:333–42.
[17] Villers A, Flamand V, Arquimedes RC, et al. Robot-assisted partial prostatectomy for anterior prostate cancer: a step-by-step guide. BJU Int 2017;119:968–74.
[18] Abdollah F, Jeong W, Dalela D, Palma-Zamora I, Sood A, Menon M. 473—Menon-precision prostatectomy (MPP): an idea, development, exploration, assessment, long-term follow-up (IDEAL) stage 1 study. Eur Urol Suppl 2019;18:e622.
[19] Zhou X., Fu B., Zhang C., et al. Transvesical robot-assisted radical prostatectomy: initial experience and surgical outcomes. BJU Int. In press. 10.1111/bju.15111.
[20] Walz J, Epstein JI, Ganzer R, et al. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: an update. Eur Urol 2016;70:301–11.
[21] Walz J, Burnett AL, Costello AJ, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol 2010;57:179–92.
[22] Vis AN, van der Poel HG, Ruiter AEC, et al. Posterior, anterior, and periurethral surgical reconstruction of urinary continence mechanisms in robot-assisted radical prostatectomy: a description and video compilation of commonly performed surgical techniques. Eur Urol 2019;76:814–22.
[23] Desai MM, Aron M, Berger A, et al. Transvesical robotic radical prostatectomy. BJU Int 2008;102:1666–9.
[24] Maurice MJ, Kaouk JH. Single-port robot-assisted perineal prostatectomy and pelvic lymphadenectomy: step-by-step technique in a cadaveric model. J Endourol 2018;32:S93–6.
[25] Montorsi F, Wilson TG, Rosen RC, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol 2012;62:368–81.
[26] Tewari AK, Srivastava A, Huang MW, et al. Anatomical grades of nerve sparing: a risk-stratified approach to neural-hammock sparing during robot-assisted radical prostatectomy (RARP). BJU Int 2011;108(6 Pt 2):984–92.
[27] Bianchi L, Turri FM, Larcher A, et al. A novel approach for apical dissection during robot-assisted radical prostatectomy: the "collar" technique. Eur Urol Focus 2018;4:677–85.
[28] Pathak RA, Hemal AK. Management of low-risk prostate cancer in patients with enlarged glands and lower urinary tract symptoms: robotic total prostatectomy, a novel technique. World J Urol 2020;38:829–36.
[29] Capello SA, Boczko J, Patel HR, Joseph JV. Randomized comparison of extraperitoneal and transperitoneal access for robot-assisted radical prostatectomy. J Endourol 2007;21:1199–202.
[30] Akand M, Erdogru T, Avci E, Ates M. Transperitoneal versus extraperitoneal robot-assisted laparoscopic radical prostatectomy: a prospective single surgeon randomized comparative study. Int J Urol 2015;22:916–21.
[31] Dalela D, Jeong W, Prasad MA, et al. A pragmatic randomized controlled trial examining the impact of the Retzius-sparing approach on early urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2017;72:677–85.
[32] Menon M, Dalela D, Jamil M, et al. Functional recovery, oncologic outcomes and postoperative complications after robot-assisted radical prostatectomy: an evidence-based analysis comparing the Retzius sparing and standard approaches. J Urol 2018;199:1210–7.
[33] Mistretta FA, Galfano A, Di Trapani E, et al. Robot assisted radical prostatectomy in kidney transplant recipients: surgical, oncological and functional outcomes of two different robotic approaches. Int Braz J Urol 2019;45:262–72.
[34] Nyarangi-Dix JN, Radtke JP, Hadaschik B, Pahernik S, Hohenfellner M. Impact of complete bladder neck preservation on urinary continence, quality of life and surgical margins after radical prostatectomy: a randomized, controlled, single blind trial. J Urol 2013;189:891–8.
[35] de Carvalho PA, Barbosa J, Guglielmetti GB, et al. Retrograde release of the neurovascular bundle with preservation of dorsal venous complex during robot-assisted radical prostatectomy: optimizing functional outcomes. Eur Urol 2020;77:628–35.
[36] Checcucci E, Veccia A, Fiori C, et al. Retzius-sparing robot-assisted radical prostatectomy vs the standard approach: a systematic review and analysis of comparative outcomes. BJU Int 2020;125:8–16.
[37] Lim SK, Kim KH, Shin TY, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: combining the best of retropubic and perineal approaches. BJU Int 2014;114:236–44.
[38] Lee J, Kim HY, Goh HJ, et al. Retzius sparing robot-assisted radical prostatectomy conveys early regain of continence over conventional robot-assisted radical prostatectomy: a propensity score matched analysis of 1,863 patients. J Urol 2020;203:137–44.
[39] Theisen KM, Myrga JM, Hale N, et al. Excessive opioid prescribing after major urologic procedures. Urology 2019;123:101–7.

EUROPEAN UROLOGY 78 (2020) 592–602

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Surgery in Motion

Robot-assisted Cavectomy Versus Thrombectomy for Level II Inferior Vena Cava Thrombus: Decision-making Scheme and Multi-institutional Analysis

Taoping Shi[a,†], *Qingbo Huang*[a,†], *Kan Liu*[a,†], *Songliang Du*[a], *Yang Fan*[a], *Luojia Yang*[a], *Cheng Peng*[a], *Dan Shen*[a], *Zhongxin Wang*[a], *Yu Gao*[a], *Liangyou Gu*[a], *Shaoxi Niu*[a], *Qing Ai*[a], *Hongzhao Li*[a], *Fengyong Liu*[b], *Qiuyang Li*[c], *Haiyi Wang*[d], *Aitao Guo*[e], *Bin Fu*[f], *Xiaojian Yang*[g], *Xuepei Zhang*[h], *Delin Wang*[i], *Dongwen Wang*[j], *Hongqian Guo*[k], *Hengping Li*[l], *Alberto Olivero*[m], *Xeng Inn Fam*[n], *Xin Ma*[a,*], *Baojun Wang*[a,*], *Xu Zhang*[a,*]

[a] *Department of Urology, Chinese PLA General Hospital/PLA Medical School, Beijing, China;* [b] *Department of Interventional Radiology, Chinese PLA General Hospital, Beijing, China;* [c] *Department of Ultrasound, Chinese PLA General Hospital, Beijing, China;* [d] *Department of Radiology, Chinese PLA General Hospital, Beijing, China;* [e] *Department of Pathology, Chinese PLA General Hospital, Beijing, China;* [f] *Department of Urology, The First Affiliated Hospital of Nanchang University, Nanchang, China;* [g] *Department of Urology, Xijing Hospital of Chinese PLA Air Force Medical University, Xi'an, China;* [h] *Department of Urology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China;* [i] *Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China;* [j] *Department of Urology, First Hospital of Shanxi Medical University, Taiyuan, China;* [k] *Department of Urology, Nanjing Drum Tower Hospital of Nanjing Medical school, Nanjing, China;* [l] *Department of Urology, Gansu Provincial Hospital, Lanzhou, China;* [m] *Department of Urology, San Martino Policlinico Hospital, University of Genova, Genoa, Italy;* [n] *Urology Unit, Surgery Department, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia*

Article info

Article history:
Accepted March 13, 2020

Associate Editor:
Alexandre Mottrie

Keywords:
Robotics
Laparoscopy
Nephrectomy
Renal cell carcinoma
Thrombus
Inferior vena cava
Vascular resection

Please visit www.europeanurology.com and www.urosource.com to view the accompanying video.

Abstract

Background: Robot-assisted thrombectomy (RAT) for inferior vena cava (IVC) thrombus (RAT-IVCT) is being increasingly reported. However, the techniques and indications for robot-assisted cavectomy (RAC) for IVC thrombus are not well described.
Objective: To develop a decision-making program and analyze multi-institutional outcomes of RAC-IVCT versus RAT-IVCT.
Design, setting, and participants: Ninety patients with renal cell carcinoma (RCC) with level II IVCT were included from eight Chinese urological centers, and underwent RAC-IVCT (30 patients) or RAT-IVCT (60 patients) from June 2013 to January 2019.
Surgical procedure: The surgical strategy was based on IVCT imaging characteristics. RAT-IVCT was performed with standardized cavotomy, thrombectomy, and IVC reconstruction. RAC-IVCT was mainly performed in patients with extensive IVC wall invasion when the collateral blood vessels were well-established. For right-sided RCC, the IVC from the infrarenal vein to the infrahepatic veins was stapled. For left-sided RCC, the IVC from the suprarenal vein to the infrahepatic veins was removed and caudal IVC reconstruction was performed to ensure the right renal vein returned through the IVC collaterals.
Measurements: Clinicopathological, operative, and survival outcomes were collected and analyzed.
Results and limitations: All procedures were successfully performed without open conversion. The median operation time (268 vs 190 min) and estimated blood loss (1500 vs 400 ml) were significantly greater for RAC-IVCT versus RAT-IVCT (both $p < 0.001$). IVC invasion was a risk factor for progression-free and overall survival at midterm follow-up. Large-volume and long-term follow-up studies are needed.
Conclusions: RAC-IVCT or RAT-IVCT represents an alternative minimally invasive approach for selected RCC patients with level II IVCT. Selection of RAC-IVCT or RAT-IVCT is mainly based on preoperative IVCT imaging characteristics, including the presence of IVC wall invasion, the affected kidney, and establishment of the collateral circulation.
Patient summary: In this study we found that robotic surgeries for level II inferior vena cava thrombus were feasible and safe. Preoperative imaging played an important role in establishing an appropriate surgical plan.

† These authors equally contributed to this work.
* Corresponding authors. Department of Urology, Chinese PLA General Hospital, 28 Fu Xing Road, Beijing 100853, China.
E-mail addresses: urologist@foxmail.com (X. Ma), baojun40009@126.com (B. Wang), xzhang@foxmail.com (X. Zhang).

https://doi.org/10.1016/j.eururo.2020.03.020
0302-2838/

1. Introduction

Locally advanced renal cell carcinoma (RCC) with inferior vena cava thrombus (IVCT) is one of the most challenging situations in urological surgery [1,2]. Although open surgery is the standard approach [2], the safety and feasibility of robot-assisted thrombectomy (RAT) for level I–IV IVCT have been reported [3–9]. RAT-IVCT was performed with satisfactory outcomes in most cases [1,10]. However, IVC resection is justified in some circumstances, including distal unresectable bland thrombosis and tumor infiltration into the IVC wall, to avoid thrombus shedding and achieve satisfactory tumor control [10–14]. Nevertheless, decisions on whether to perform partial or circumferential IVC resection (the latter is known as cavectomy) are generally made intraoperatively during thrombectomy [10]. In patients without well-established collateral blood vessels, cavectomy in acute situations may cause hypotension due to a decrease in venous return and postoperative renal insufficiency, lower extremity edema, or abdominal wall varicosity [10,13]. Therefore, in this study our aim was to develop a decision-making scheme and to analyze operative and survival outcomes for robot-assisted cavectomy (RAC)-IVCT and RAT-IVCT.

2. Patients and methods

2.1. Patients

Ninety patients with RCC and level II IVCT who underwent RAC-IVCT or RAT-IVCT between June 2013 and January 2019 were included from eight Chinese urological centers (Supplementary Table 1). Surgeons from the Chinese PLA General Hospital designed the surgical strategy and provided support for the surgical technique; the other centers managed patients according to their surgical strategy. The study received institutional review board approval and inter-institutional data-sharing agreements were established as required. Tumor thrombus was categorized according to the Mayo Clinic classification [1]. Postoperative complications were graded according to the modified Clavien-Dindo scheme [15].

2.2. Preoperative assessment

Enhanced magnetic resonance imaging (MRI) was performed within 1 wk before surgery to assess the features of the primary tumor and IVC thrombus, including local tumor invasion, tumor size, thrombus length, bland thrombus, and IVC wall infiltration. For all IVCTs involving more than two-thirds of the IVC lumen, cavography was performed to evaluate establishment of the collateral blood vessels. For cavography, the modified Seldinger technique was used. Specifically, the right femoral vein was punctured to allow insertion of a 4-F catheter sheath. Then a pigtail catheter (Terumo, Tokyo, Japan) was inserted through the sheath to perform IVC angiography (MIYABI; Siemens, Erlangen, Germany). Iodized oil (20 ml; Guerbet, Villepinte, France) was administered as a contrast agent via quick-push injection (200 psi, 4 ml/s, 4 s; Supplementary Fig. 1).

2.3. Decision-making scheme

We developed a decision-making scheme to guide surgical treatment for RCC with level II IVCT according to three parameters: the location of the primary tumor, the presence of IVC wall invasion, and establishment of IVC collateral blood vessels (Fig. 1). For right-sided RCC, RAC-IVCT was performed in cases with suspected IVC wall invasion and/or well-established collaterals (21 cases). There were six cases of right-sided RCC associated with well-established collaterals but the absence of IVC wall invasion; for five of these cases, unresectable bland thrombus was found in the distal IVC. For left-sided RCC, owing to the lack of collaterals in the right renal veins, segmental transection of the IVC without reconstruction may cause renal dysfunction. RAC-IVCT was only performed for patients with IVCT with extensive IVC wall invasion and well-established IVC collaterals (9 cases). The other 60 cases underwent RAT-IVCT. The main collaterals were located and carefully preserved under intraoperative ultrasound guidance; IVC wall invasion was inspected under direct vision for adhesion and infiltration was later confirmed via pathological examination (Fig. 2). When the IVC is completely occluded by thrombus, venous return flows through the caudal IVC, lumbar vein, and lumbar ascending vein to the hemiazygos and azygos vein systems (Fig. 3).

2.4. Preoperative preparation

Preoperative targeted therapies were given selectively to patients with metastatic disease with the intention to downgrade thrombus levels. In detail, sunitinib 50 mg (SUTENT, Pfizer, New York, NY, USA) was given orally for a 6-wk cycle (4 wk followed by a break of 2 wk). After three cycles of therapy, the feasibility of surgery and the surgical strategy were reevaluated. Preoperative intravenous heparin was started on diagnosis to prevent thrombus extension and embolization. Renal artery embolization on the affected side was conducted 1–2 h preoperatively in patients with left-sides RCC or large right-sided renal tumors.

2.5. Surgical technique

For RAT-IVCT, standard cavotomy, thrombectomy, and IVC reconstruction were performed [3,4]. For RAC-IVCT, we performed cavectomy without the IVC replacement technique.

2.5.1. RAC-IVCT for right-sided RCC with IVCT

Fig. 4 shows the key RAC-IVCT steps for right-sided RCC with IVCT. The procedures are presented in Supplementary Video 1. The cephalic IVC below the hepatic veins was stapled using Endo GIA (Covidien, Minneapolis, MN, USA), leaving a minimal segment of cava caudal to the hepatic veins, thereby limiting turbulence and potential thrombosis.

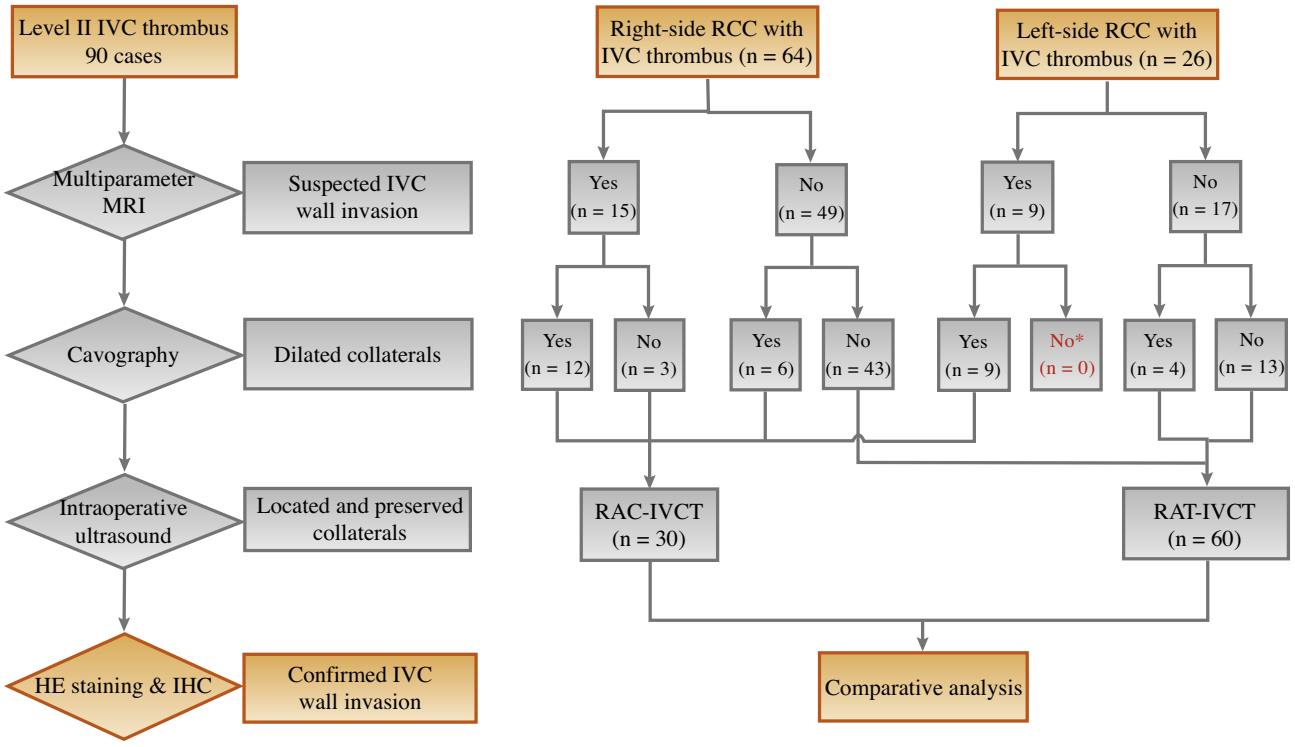


Fig. 1 – Decision-making scheme for surgical treatments for renal cell carcinoma (RCC) with level II inferior vena cava thrombus (IVCT). Enhanced magnetic resonance imaging (MRI) was performed within 1 wk before surgery to assess features of the primary tumor and IVCT, specifically local tumor invasion and IVC wall infiltration. For all IVCT cases involving more than two-thirds of the IVC lumen, cavography was performed to evaluate establishment of the collateral blood vessels. The main collaterals were carefully preserved under intraoperative ultrasound guidance, and IVC wall invasion was confirmed by pathological examination. The surgical strategy (RAC-IVCT vs RAT-IVCT) was planned according to the tumor location, extent of IVC wall infiltration, and collateral establishment. Finally, the operative and survival outcomes for RAC-IVCT versus RAT-IVCT were analyzed. MRI = magnetic resonance imaging; HE = hematoxylin-eosin; IHC = immunohistochemistry.

Subsequently, the left renal vein was circumferentially dissected, looped, and stapled. The right renal artery was exposed and ligated in the inter-aortocaval space. The caudal tumor-bearing IVC was further dissected circumferentially by clipping some lumbar veins. The main collaterals were carefully preserved under intraoperative ultrasound guidance during caudal IVC stapling.

2.5.2. *RAC-IVCT for left-sided RCC with IVCT*

Fig. 5 shows the key RAC-IVCT steps for left-sided RCC with IVCT. The procedures are presented in Supplementary Video 2. The cephalic IVC and left renal vein were sequentially stapled. The IVC was dissected retrogradely and circumferentially. The vessel loops were wrapped twice around the IVC between the superior border of the right renal vein and the inferior border of the left renal vein. The IVC wall was cut 1–2 cm cephalic to the loop; with precautions taken to preserve the orifice of preexisting collaterals. Then the caudal IVC was reconstructed to ensure right renal venous return through the IVC collaterals.

2.6. *Postoperative treatment and follow-up*

Anticoagulants were routinely prescribed for 6 mo after caval resection. Adjuvant targeted therapies were given to patients with metastatic disease or residual lesion. Sunitinib 50 mg was given orally for a 6-wk cycle. After three cycles, sunitinib 25 mg daily was then prescribed as indicated. Computed tomography or MRI of the chest, abdomen, and pelvis, as well as venous ultrasonography of the lower extremities, was performed every 3–6 mo until the latest follow-up visit or death.

2.7. *Statistical analysis*

Results for continuous variables are presented as the median and range or interquartile range (IQR), with analysis by *t*-test or analysis of variance after estimating the variance between groups. Results for categorical variables are presented as the frequency count and percentage, with analysis by χ^2 test. The Kaplan-Meier method and log-rank test were used to estimate and compare the probability of progression-free survival (PFS) and overall survival (OS). All statistical analyses were performed with PASW Statistics software 18.0 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ considered statistically significant.

3. Results

Demographic data are outlined in Table 1. RAC-IVCT was performed in 30 patients (21 right-sided and 9 left-sided RCC) and RAT-IVCT in 60 patients (44 right-sided and

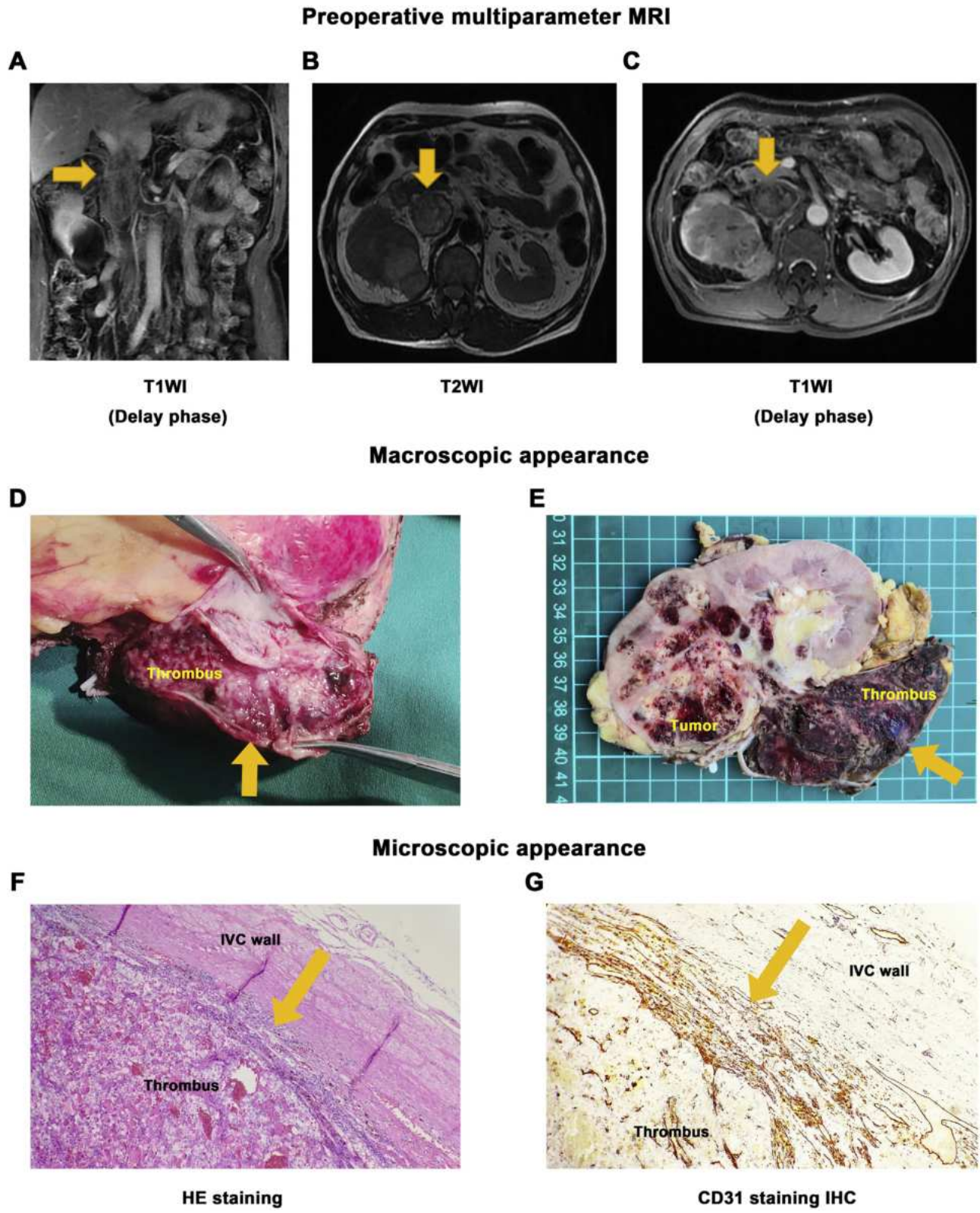


Fig. 2 – Inferior vena cava (IVC) wall infiltration was assessed using preoperative multiparameter magnetic resonance imaging (MRI), evaluation of the macroscopic appearance, and microscopic examination. (A–C) Preoperative multiparameter MRI scans showed signs of IVC wall infiltration, characterized by breaking of the IVC wall (yellow arrow) on (A) coronal delayed-phase T1-weighted imaging (T1WI), (B) axial T2WI, and (C) axial delayed-phase T1WI. Macroscopic appearance of (D) a fresh specimen and (E) a formalin-fixed specimen. Microscopic examination of the IVC thrombus after (F) hematoxylin-eosin (HE) staining and (G) immunohistochemistry (IHC) staining with the endothelium-specific marker CD31.

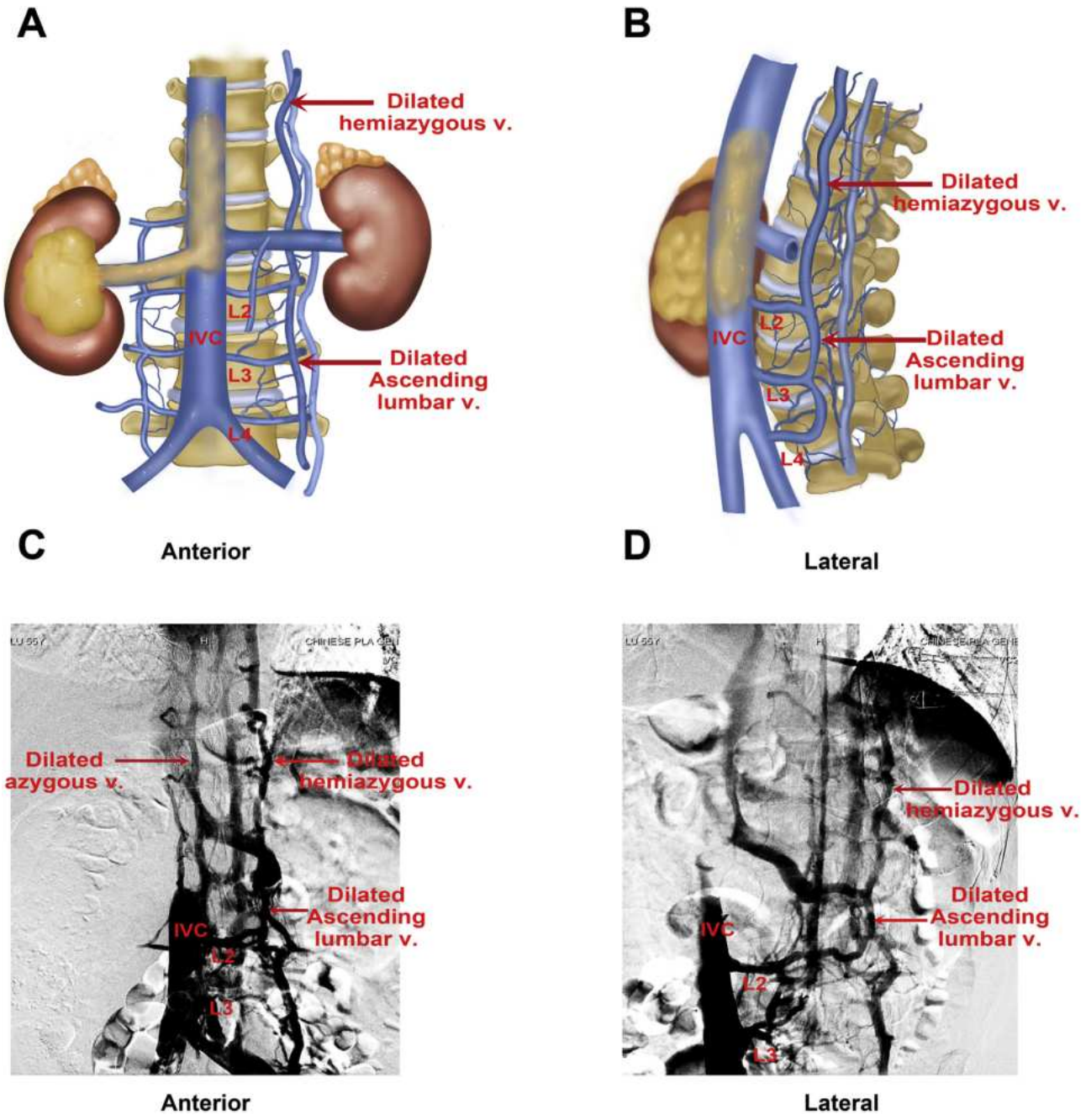


Fig. 3 – Schematic drawing and cavography images of the collateral circulation for a caudal inferior vena cava (IVC) incrementally occluded by a thrombus. (A,B) Diagram illustrating the collateral circulation through the caudal IVC to the dilated lumbar vein (v.), ascending lumbar vein, and hemiazygous and azygous veins. (C,D) Cavography images showing the collateral circulation through the caudal IVC to the dilated lumbar vein, ascending lumbar vein, and hemiazygous and azygous veins.

16 left-sided RCC). The RAC-IVCT group had higher tumor grade, longer IVC thrombi, and high rates of IVC wall invasion, distant metastasis and combination of bland thrombus. No significant differences were noted for demographic characteristics (age, gender, and body mass index) or tumor location, size, and type.

Table 2 presents results for perioperative outcomes and complications. The median operation time was significantly longer for RAC-IVCT than for RAT-IVCT (268 vs 190 min; $p <$ 0.001). RAC-IVCT for left-sided RCC took longer than for right-sided RCC in both groups. The median estimated blood loss was 1500 ml (IQR 970–2000) of RAC-IVCT, which was significantly greater than the 400 ml (IQR 200–1000) for RAT-IVCT. Twenty-three patients (76.7%) received an intraoperative blood transfusion in the RAC-IVCT group, while only 12 patients (20%) in the RAT-IVCT group needed a blood transfusion. Renal function was successfully preserved for the patients in both groups.

In the RAT-IVCT group, only mild complications (grades I and II) occurred. However, more complications were

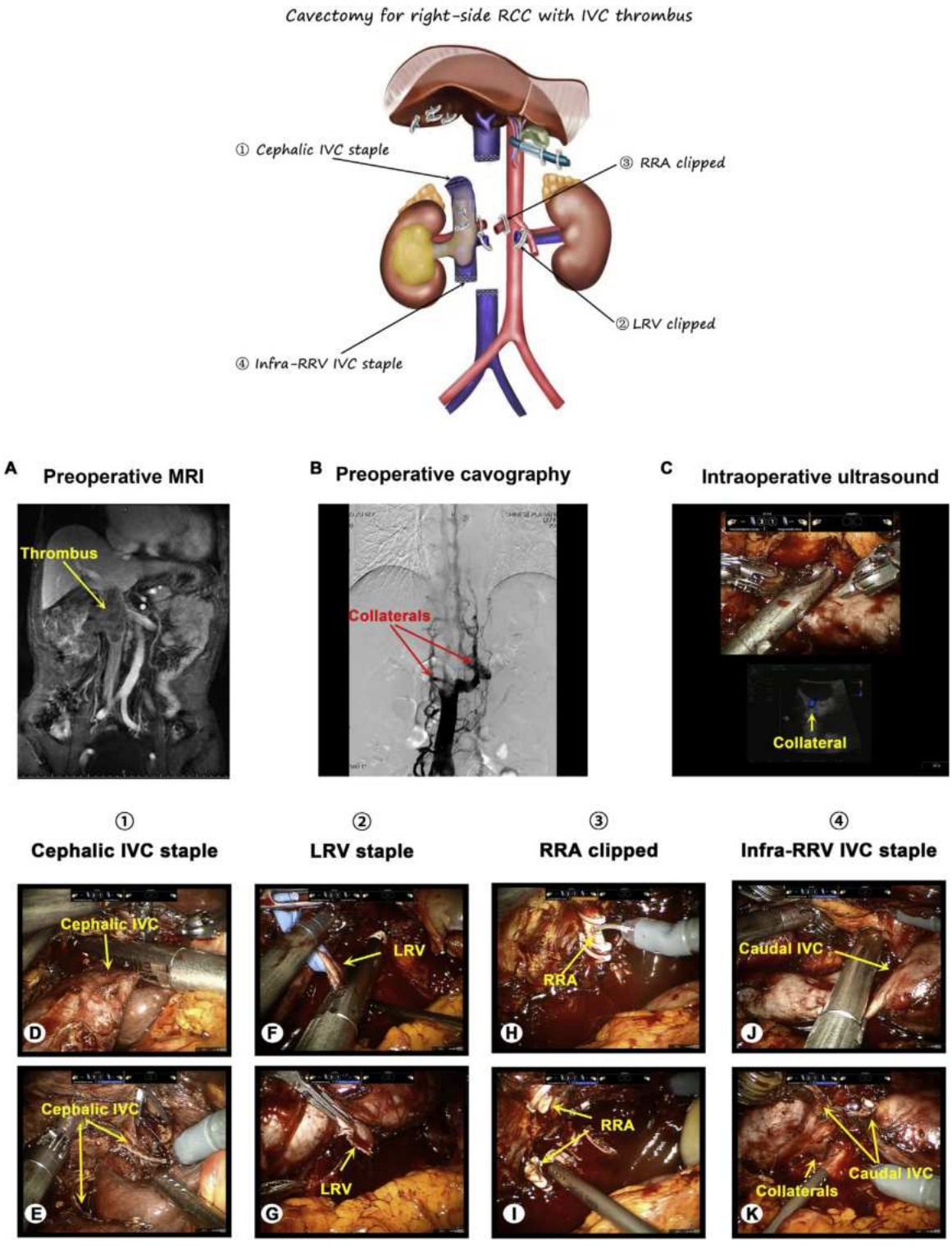


Fig. 4 – Key steps in robot-assisted cavectomy (RAC) for right-sided RCC with inferior vena cava thrombus (IVCT). Schematic showing the sequential ligation order: cephalic IVC above the thrombus end, left renal vein (LRV), right renal artery (RRA), and infra-right renal vein (RRV) IVC (upper panel). Surgical procedure for RAC-IVCT for a case of right-sided RCC with IVCT (lower panel). (A) Preoperative multiphase magnetic resonance imaging (MRI) showed a case of right-sided RCC with level II IVCT filling the entire caval lumen. (B) IVC cavography showed venous return through well-established venous collaterals. (C) Intraoperative ultrasound imaging identified the main collaterals that should be carefully preserved. (D–K) Robot-assisted resection for right-sided RCC with IVCT. (D,E) The cephalic IVC was stapled below the hepatic veins. (F,G) The LRV was stapled at the insertion of the IVC. (H,I) The RRA was clipped and incised. (J,K) The caudal IVC was stapled below the thrombus and the main collateral vessel was carefully preserved.

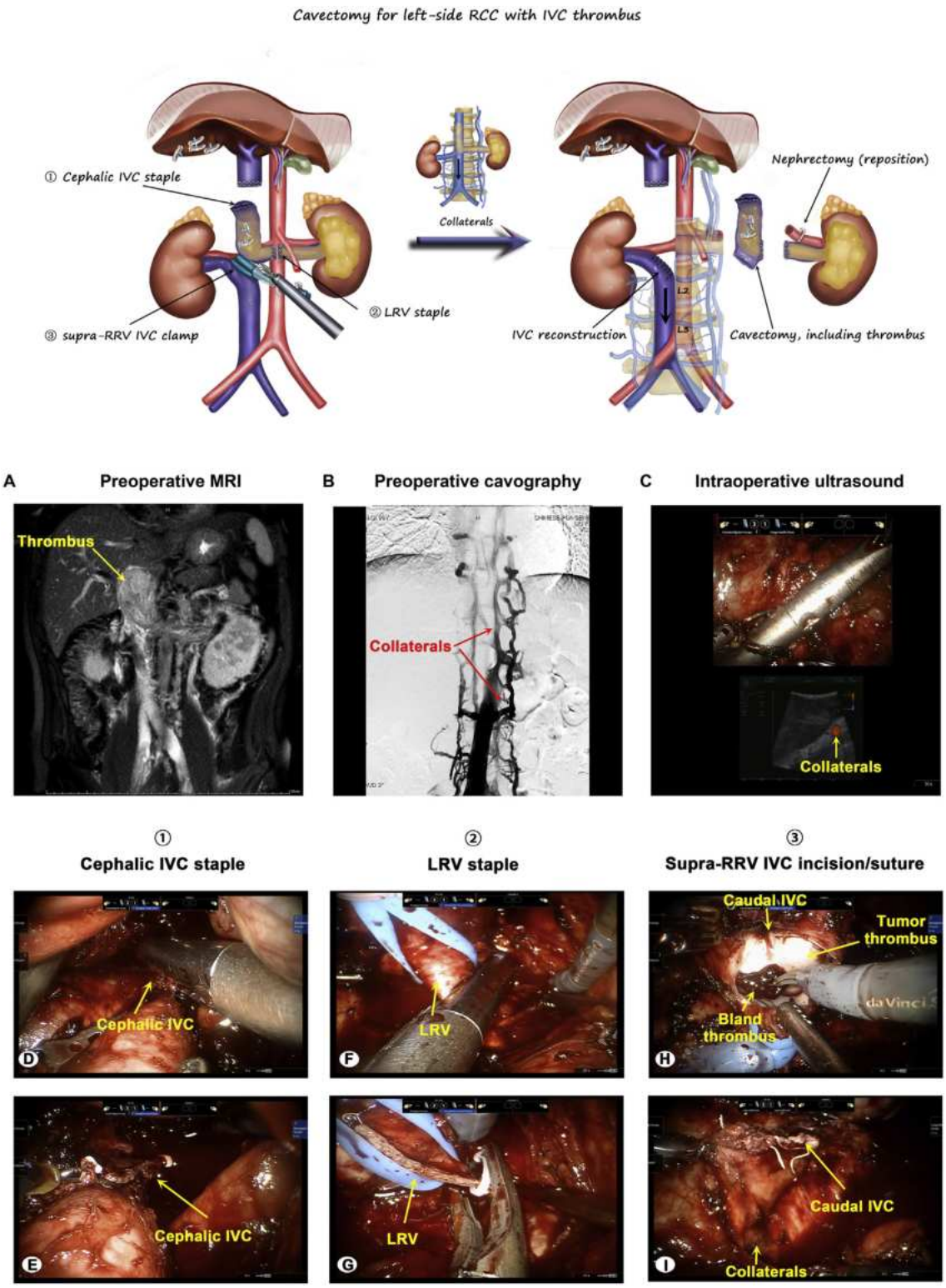


Fig. 5 – Key steps in robot-assisted cavectomy (RAC) for left-sided renal cell carcinoma (RCC) with inferior vena cava thrombus (IVCT). Schematic showing the sequential ligation order and collateral circulation (upper panel). The cephalic IVC above the thrombus end and the left renal vein (LRV) including the thrombus were stapled. The IVC was occluded and incised at the superior margin of the right renal vein (RRV) (left). The caudal IVC was reconstructed with a two-layer continuous suture. The patient was repositioned for left nephrectomy. As described in Fig. 3, venous return of the RRV was through the caudal IVC, lumbar vein, and lumbar ascending vein to the hemiazygous and azygous vein systems (right). Arrows indicate the direction of venous blood. Surgical procedure for RAC-IVCT for a case of left-sided RCC with IVCT (lower panel). (A) Preoperative multiphase magnetic resonance imaging showed left-sided RCC with level II IVCT. The IVC was occupied and distended by the thrombus. (B) IVC cavography showed that the collateral vessels were well established. (C) Intraoperative ultrasound imaging identified the main collaterals that should be carefully preserved. (D–I) Robot-assisted resection for a case of left-sided RCC with IVCT. (D,E) The cephalic IVC was stapled below the hepatic veins. (F,G) The LRV including the thrombus was stapled using Endo GIA. (H,I) The caudal IVC was looped and tightened above the RRV using the Rummel tourniquet technique. (H) The IVC wall was incised and the thrombosed IVC was removed. (I) The IVC was reconstructed with Gore-tex sutures and the main collateral vessel was carefully preserved.

Table 1 – Comparison of patient baseline characteristics.

Characteristic	RAC-IVCT (*n* = 30)	RAT-IVCT (*n* = 60)	*p* value
Median age, yr (range)	53.2 (36–76)	56.2 (23-86)	0.323
Gender, male/female, n	22/8	44/16	1.000
Mean body mass index, kg/m^2 (range)	24.5 (18.9–29.7)	24.4 (13.2–31.8)	0.889
Affected kidney, left/right, *n*	9/21	17/43	1.000
Tumor type, ccRCC/pRCC, *n*	25/5	52/8	0.635
Tumor grade, I/II/III, *n*	6/14/10	31/22/7	0.000*
Mean renal tumor size, cm, (range)	8.6 (2.5-19.0)	7.7 (2.0-16.0)	0.211
Mean thrombus length, cm (range)	7.1 (3-12.8)	4.2 (2.1-11.0)	<0.001*
Perirenal fat invasion, *n* (%)	8 (26.7)	8 (13.3)	0.051
IVC wall invasion, n (%)	17 (56.7)	1 (1.7)	<0.001*
Presence of bland thrombus, *n* (%)	5 (16.7)	2 (3.3)	0.005*
Lymph node metastasis, *n* (%)	4 (13.3)	8 (13.3)	1.000
Distant metastasis, *n* (%)	6 (20)	5 (8.3)	0.046*
Preoperative targeted therapy, *n* (%)	5 (16.7)	10 (16.7)	1.000
Adjuvant targeted therapy, *n* (%)	14 (46.7)	22 (36.7)	0.364

ccRCC = clear cell renal cell carcinoma; pRCC = papillary renal cell carcinoma; IVC = inferior vena cava; RAC = robot-assisted cavectomy; IVCT = IVC thrombus; RAT = robot-assisted thrombectomy.
* Statistically significant difference.

Table 2 – Comparison of operative outcomes and complications.

Characteristic	RAC-IVCT	RAT-IVCT	*p* value
Median operative time, min (IQR)	268 (238–320)	190 (150–270)	<0.001*
Right side	260 (235–320)	160 (135–205)	
Left side	300 (238–339)	322 (269–366)	
Median estimated blood loss, ml (IQR)	1500 (975_2000)	400 (200–1000)	0.001*
Patients receiving transfusion, *n* (%)	23 (81.5)	12 (81.5)	
Transfer to intensive care unit, *n* (%)	24 (85.2)	14 (85.2)	
Mean time to surgical drain removal, d (range)	4 (4–7)	3 (4–7)	
Mean time to full ambulation, d (range)	3 (2–7)	3 (2–6)	
Mean time to oral feeding, d (range)	3 (3–5)	3 (2–6)	
Mean postoperative hospital stay, d (range)	7 (4–23)	7 (3–12)	
Perioperative complications, *n* (%)[a]			<0.001*
Grade I	4	3	
Grade II	7	4	
Grade III	2	0	
Grade IV	0	0	

IQR = interquartile range; RAC = robot-assisted cavectomy; IVCT = inferior vena cava thrombus; RAT = robot-assisted thrombectomy.
* Statistically significant difference.
[a] According to the Clavien classification of surgical complications [11].

observed in the RAC-IVCT group. Two grade III complications (1 case of bleeding from spleen injury and 1 case of fistula from intestinal injury) occurred in the RAC-IVCT group and were managed via reoperation. Seven patients developed mild transient lower-extremity edema and recovered within 1 mo. One death due to cardiac arrest 2 wk after surgery occurred for a patient with preexisting coronary heart disease. In the RAC-IVCT group, postoperative cavography was performed in four cases during 3-mo follow-up and revealed good collateral circulation preservation in comparison with preoperative findings (Supplementary Fig. 2).

The median follow-up was 18 mo (range 1–75). In the RAC-IVCT group, new-onset metastasis occurred in 19 patients (63.3%) postoperatively, resulting in 13 deaths (43.3%). In the RAT-IVCT group, new-onset metastasis occurred in 17 patients (28.3%) postoperatively, resulting in six deaths (10%). Survival analysis revealed that among patients with IVC wall invasion, OS and PFS were poor (Fig. 6A,B). The other factors associated with both OS and PFS included tumor size and grade, perirenal fat invasion, and lymph node and distant metastases (Fig. 6C–L). However, tumor type and preoperative and postoperative targeted therapies were not associated with either OS or PFS (Supplementary Fig. 3).

4. Discussion

We developed a preoperative decision-making scheme to tailor the surgical strategy for IVCT in RCC. We introduced a technique for RAC-IVCT and analyzed operative and oncological outcomes for a multi-institutional cohort. We demonstrated that RAC-IVCT is feasible and safe for RCC patients with extensive IVC wall invasion and well-established venous collaterals.

RAT-IVCT has been increasingly reported using a standardized technique involving cavotomy, thrombectomy, and IVC reconstruction [3–9]. However, for patients

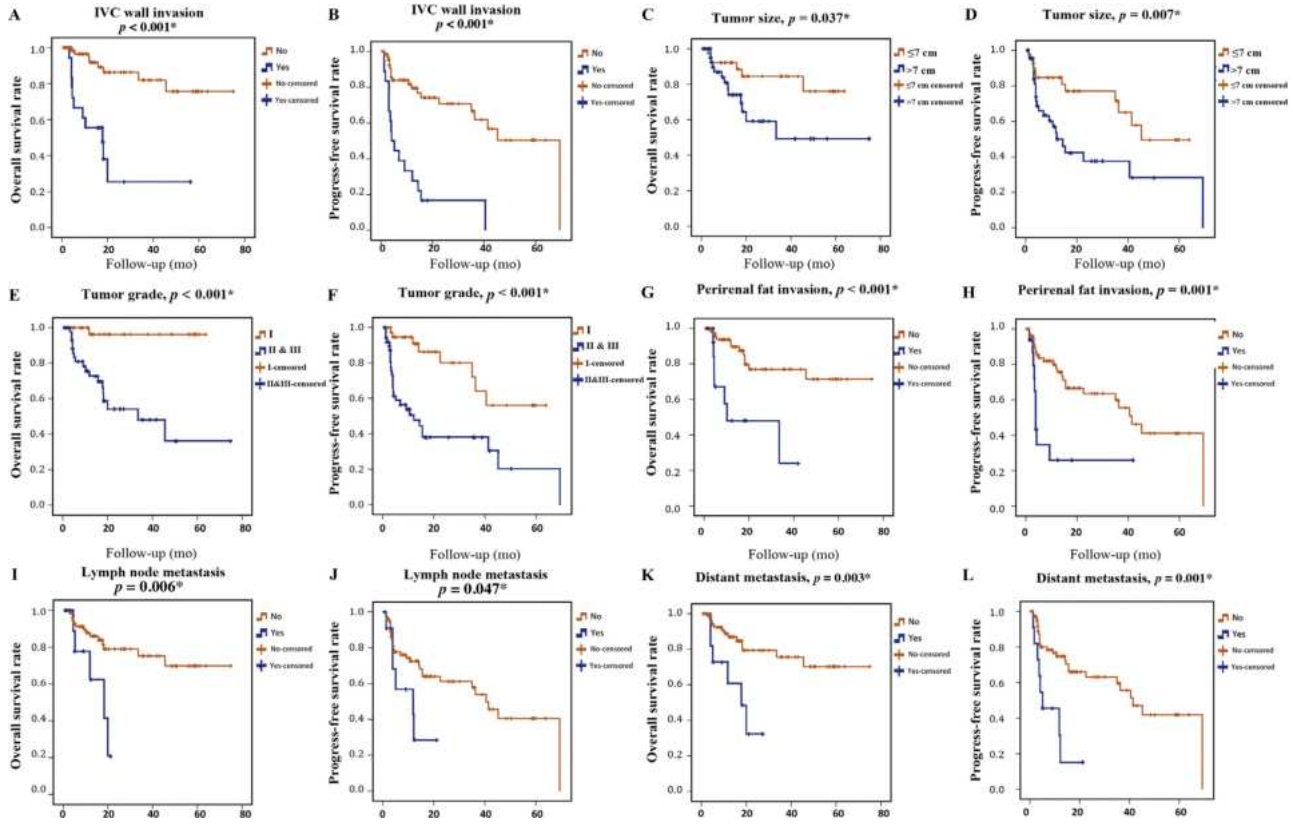


Fig. 6 – Factors associated with overall survival (OS) and progression-free survival (PFS) analyzed using Kaplan-Meier survival curves and compared between groups using the log-rank test. Tumor size and thrombus length were transformed into binary data at a threshold of 7 cm (≤7 cm vs >7 cm). Tumor grade was grouped as grade I versus grades II and III. The results show that inferior vena cava (IVC) wall invasion, tumor size, tumor grade, perirenal fat invasion, lymph node metastasis and distant metastasis were associated with both OS and PFS.

with tumor infiltration into the IVC wall, partial or circumferential IVC resection with IVC reconstruction is indicated [10,13,16] as IVC wall invasion is a factor indicating poor prognosis [17–19]. Venous wall invasion was associated with a nearly six-fold increase in the risk of death from RCC in a multivariate analysis controlling for tumor size, stage, and thrombus level [20]. In this series, 20% (18/90) of cases of IVC wall invasion were confirmed on pathological examination. Our results also show that IVC wall invasion was associated with poor OS and PFS, which further indicates that RAC-IVCT was the optimal strategy. This minimally invasive approach fulfils the principle of oncology surgery, and is feasible and safe for patients without preexisting cardiac dysfunction and with well-established collateral blood vessels. In patients with IVC wall invasion without established collateral vessels, IVC reconstruction was required. The reconstruction techniques available vary from patch angioplasty to IVC graft replacement, typically with a polytetrafluoroethylene graft or autogenous vein grafts [21,22]. Chopra et al [6] reported their experience with robotic IVC patch angioplasty after partial IVC resection. We recommend the open approach if segmental IVC replacement is required, as this is a complex and time-consuming procedure that requires cooperation between urologists and vascular surgeons.

The critical issue in IVCT management is the development of a decision-making algorithm to tailor the operative technique. According to the literature, approximately 8.1–22% of patients undergoing tumor thrombectomy required segmental resection of the IVC [10,11,23]. Decisions on whether to perform partial or circumferential IVC resection are generally taken intraoperatively [10]. Furthermore, hemodynamic changes may occur after IVC resection due to impaired venous return leading to decreased cardiac output and increased peripheral venous pressure. A study on acute IVC ligation for pulmonary emboli prevention showed a 9% mortality rate, postoperative lower-extremity swelling in more than one-third of patients, and long-term venous sequelae in up to 50% [24]. Cases of resection of chronically occluded IVC with well-established collaterals have minor disturbances of hemodynamic stability. In our series, only seven of 30 patients developed mild, transient edema in the lower extremities and recovered within 1 mo. One patient dies due to cardiac arrest resulting from his preexisting coronary heart disease. Therefore, strategies should be planned properly for individual patients. Preoperative MRI plays a key role in detection and prediction of vein wall invasion, with 92% accuracy in predicting vein wall invasion [25]. Lack of experience in selecting parameters for MRI in the early stages may account for the relatively low positive predictive accuracy of 75% (18/24). It was reported that complete occlusion of the IVC lumen or vessel breach and increases in IVC diameter were associated with a higher probability of IVC wall

invasion [26]. In our experience, the most reliable indicators of invasion are thrombus hyperintensity appearing on both sides of the vessel wall in contrast-enhanced images and continuity interruption of the vessel-wall hypointensity in T2-weighted images. The exclusion criterion was lack of IVC occlusion as determined from the presence of a blood stream signal between the tumor thrombus and the IVC wall. Cavography has high sensitivity in detecting vascular tumors and yields significant information for evaluation of the collateral circulation [16,27]. The presence of large venous collaterals provides vital clues regarding IVC patency. Other than partial nephrectomy, we have also accumulated experience in using intraoperative ultrasound to determine the thrombus ends and detecting the presence of IVC wall invasion and bland thrombus [4,5,28]. In this study, intraoperative ultrasound was used in locating and preserving the main collaterals to reduce the risk of severe lower-extremity edema and a decrease in cardiac output.

As previously described, one factor that must be considered is the affected kidney side for RAT-IVCT [3] and RAC-IVCT. For right-sided RCC, the thrombus was removed en bloc, which did not compromise the left renal venous return owing to the nature of existing collaterals, mainly through the hemiazygos or azygos system [21,29]. However, experience with resection for left-sided RCC is limited owing to concerns regarding renal dysfunction due to right renal vein occlusion. In this study, we showed that resection could be safely performed for IVCT in left-sided RCC. IVC resection in left-sided RCC should be preceded by the effort collateral circulation preservation through caudal IVC. Long-term postoperative anticoagulation was performed in all patients who have undergone RAC-IVCT.

In comparison to RAT-IVCT, we found that RAC-IVCT was often used for more complicated conditions characterized by higher tumor grade, longer IVC thrombi, a higher perirenal fat invasion ratio, IVC wall invasion, distant metastasis, and a combination of bland thrombus. Thus, operation time, blood loss, and complications were significantly greater in the RAC-IVCT group than for RAT-IVCT. At midterm follow-up, OS and PFS were worse among RAC-IVCT than among RAT-IVCT patients. Nevertheless, selection bias for the two groups may account for the difference in oncological outcomes. In accordance with a previous study [30], our result showed that characteristics such as tumor size and grade, IVC invasion, peripheral fat invasion, and lymph node or distant metastases were associated with PFS and OS.

5. Conclusions

In this retrospective study we described the operative and oncological outcomes for two robotic approaches for level II IVCT. Future large-volume studies comparing RAC-IVCT and IVC replacement with the open counterpart approach over long-term follow-up are required to further analyze the feasibility and advantages of RAC-IVCT.

RAC-IVCT and RAT-IVCT are two minimally invasive approaches for RCC patients with level II IVCT. Selection of the surgical strategy is mainly based on preoperative IVCT imaging characteristics, including the presence of IVC wall invasion, the affected kidney, and establishment of the collateral circulation.

Author contributions: Xu Zhang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shi, Xu Zhang, Ma, B. Wang.
Acquisition of data: Shi, Huang, K. Liu, L. Yang, Gao, Gu, Niu, Xuepei Zhang, X. Yang, Fu, Delin Wang, Dongwen Wang, H. Guo, Hengping Li.
Analysis and interpretation of data: Shi, Huang, K. Liu, Du, Fan.
Drafting of the manuscript: Shi, Huang, Du, K. Liu, Fan.
Critical revision of the manuscript for important intellectual content: Olivero, Fam, Xu Zhang, Ma, B. Wang.
Statistical analysis: Shi, Huang, Fan, Peng, Shen, Z. Wang, L. Yang.
Obtaining funding: Huang, Xu Zhang, B. Wang, Ma.
Administrative, technical, or material support: Ai, Hongzhao Li, F. Liu, Q. Li, Guodong Zhao, H. Wang, A. Guo.
Supervision: Xu Zhang, Ma, B. Wang.
Other: None.

Financial disclosures: Xu Zhang certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** The project was supported by the Natural Science Foundation of Beijing Municipality (grant no. 7194319) and the National Natural Science Foundation of China (grant nos. 81970594,81970665, and81972389). The sponsors played a role in the design and conduct of the study, data collection, and preparation of the manuscript.

CRediT authorship contribution statement

Taoping Shi: Conceptualization, Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Qingbo Huang:** Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition. **Kan Liu:** Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Songliang Du:** Writing - original draft, Formal analysis. **Yang Fan:** Writing - original draft, Data curation, Formal analysis. **Luojia Yang:** Data curation, Formal analysis. **Cheng Peng:** Data curation, Formal analysis. **Dan Shen:** Data curation, Formal analysis. **Zhongxin Wang:** Formal analysis, Validation. **Yu Gao:** Data curation. **Liangyou Gu:** Data curation. **Shaoxi Niu:** Data curation. **Qing Ai:** Methodology. **Hongzhao Li:** Methodology, Validation. **Fengyong Liu:** Investigation. **Qiuyang Li:** Investigation. **Haiyi Wang:** Investigation. **Aitao Guo:** Investigation. **Bin Fu:** Resources, Data curation. **Xiaojian Yang:** Resources, Data curation. **Xuepei Zhang:** Resources, Data curation. **Delin Wang:** Resources, Data curation. **Dongwen Wang:** Resources, Data curation. **Hongqian Guo:** Resources, Data curation. **Hengping Li:** Resources,

Data curation. **Alberto Olivero:** Writing - review & editing. **Xeng Inn Fam:** Writing - review & editing. **Xin Ma:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Baojun Wang:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Xu Zhang:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at doi:https://doi.org/10.1016/j.eururo.2020.03.020 and via www.europeanurology.com.

References

[1] Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int 2004;94:33–41.

[2] Abaza R. Initial series of robotic radical nephrectomy with vena caval tumor thrombectomy. Eur Urol 2011;59:652–6.

[3] Wang B, Li H, Ma X, et al. Robot-assisted laparoscopic inferior vena cava thrombectomy: different sides require different techniques. Eur Urol 2016;69:1112–9.

[4] Wang B, Li H, Huang Q, et al. Robot-assisted retrohepatic inferior vena cava thrombectomy: first or second porta hepatis as an important boundary landmark. Eur Urol 2018;74:512–20.

[5] Wang B, Huang Q, Liu K, et al. Robot-assisted level III–IV inferior vena cava thrombectomy: initial series with step-by-step procedures and 1-yr outcomes. Eur Urol 2020;78:77–86.

[6] Chopra S, Simone G, Metcalfe C, et al. Robot-assisted level II–III inferior vena cava tumor thrombectomy: step-by-step technique and 1-year outcomes. Eur Urol 2016;72:267–74.

[7] Gill IS, Metcalfe C, Abreu A, et al. Robotic level III inferior vena cava tumor thrombectomy: initial series. J Urol 2015;194:929–38.

[8] Ramirez D, Maurice MJ, Cohen B, Krishnamurthi V, Haber GP. Robotic level III IVC tumor thrombectomy: duplicating the open approach. Urology 2016;90:204–7.

[9] Bratslavsky G, Cheng JS. Robotic-assisted radical nephrectomy with retrohepatic vena caval tumor thrombectomy (level III) combined with extended retroperitoneal lymph node dissection. Urology 2015;86:1235–40.

[10] Psutka SP, Boorjian SA, Thompson RH, et al. Clinical and radiographic predictors of the need for inferior vena cava resection during nephrectomy for patients with renal cell carcinoma and caval tumour thrombus. BJU Int 2015;116:388–96.

[11] Blute ML, Boorjian SA, Leibovich BC, Lohse CM, Frank I, Karnes RJ. Results of inferior vena caval interruption by greenfield filter, ligation or resection during radical nephrectomy and tumor thrombectomy. J Urol 2007;178:440–5.

[12] Ayyathurai R, Garcia-Roig M, Gorin MA, et al. Bland thrombus association with tumour thrombus in renal cell carcinoma: analysis of surgical significance and role of inferior vena caval interruption. BJU Int 2012;110:E449–55.

[13] Caso J, Seigne J, Back M, Spiess PE, Pow-Sang J, Sexton WJ. Circumferential resection of the inferior vena cava for primary and recurrent malignant tumors. J Urol 2009;182:887–93.

[14] Shirodkar SP, Ciancio G, Soloway MS. Vascular stapling of the inferior vena cava: further refinement of techniques for the excision of extensive renal cell carcinoma with unresectable vena-caval involvement. Urology 2009;74:846–50.

[15] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

[16] Yoshidome H, Takeuchi D, Ito H, et al. Should the inferior vena cava be reconstructed after resection for malignant tumors? Am J Surg 2005;189:419–24.

[17] Sevinc M, Kirkali Z, Yorukoglu K, Mungan U, Sade M. Prognostic significance of microvascular invasion in localized renal cell carcinoma. Eur Urol 2000;38:728–33.

[18] Van Poppel H, Vandendriessche H, Boel K, et al. Microscopic vascular invasion is the most relevant prognosticator after radical nephrectomy for clinically nonmetastatic renal cell carcinoma. J Urol 1997;158:45–9.

[19] Rodriguez Faba O, Linares E, Tilki D, et al. Impact of microscopic wall invasion of the renal vein or inferior vena cava on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus: a multi-institutional analysis from the International Renal Cell Carcinoma-Venous Thrombus Consortium. Eur Urol Focus 2018;4:435–41.

[20] Zini L, Destrieux-Garnier L, Leroy X, et al. Renal vein ostium wall invasion of renal cell carcinoma with an inferior vena cava tumor thrombus: prediction by renal and vena caval vein diameters and prognostic significance. J Urol 2008;179:450–4.

[21] Gonzalez J, Gorin MA, Garcia-Roig M, Ciancio G. Inferior vena cava resection and reconstruction: technical considerations in the surgical management of renal cell carcinoma with tumor thrombus. Urol Oncol 2014;32, 34.e19–26.

[22] Bower TC, Nagorney DM, Cherry Jr KJ, et al. Replacement of the inferior vena cava for malignancy: an update. J Vasc Surg 2000;31:270–81.

[23] Lue K, Russell CM, Fisher J, et al. Predictors of postoperative complications in patients who undergo radical nephrectomy and IVC thrombectomy: a large contemporary tertiary center analysis. Clin Genitourin Cancer 2016;14:89–95.

[24] Donaldson MC, Wirthlin LS, Donaldson GA. Thirty-year experience with surgical interruption of the inferior vena cava for prevention of pulmonary embolism. Ann Surg 1980;191:367–72.

[25] Aslam Sohaib SA, Teh J, Nargund VH, Lumley JS, Hendry WF, Reznek RH. Assessment of tumor invasion of the vena caval wall in renal cell carcinoma cases by magnetic resonance imaging. J Urol 2002;167:1271–5.

[26] Adams LC, Ralla B, Bender YY, et al. Renal cell carcinoma with venous extension: prediction of inferior vena cava wall invasion by MRI. Cancer Imaging 2018;18:17.

[27] Liu D, Ren HL, Liu B, et al. Renal function preservation in surgical resection of primary inferior vena cava leiomyosarcoma involving the renal veins. Eur J Vasc Endovasc Surg 2018;55:229–39.

[28] Li QY, Li N, Huang QB, et al. Contrast-enhanced ultrasound in detecting wall invasion and differentiating bland from tumor thrombus during robot-assisted inferior vena cava thrombectomy for renal cell carcinoma. Cancer Imaging 2019;19:79.

[29] Duty B, Daneshmand S. Resection of the inferior vena cava without reconstruction for urologic malignancies. Urology 2009;74:1257–62.

[30] Abel EJ, Masterson TA, Karam JA, et al. Predictive nomogram for recurrence following surgery for nonmetastatic renal cell cancer with tumor thrombus. J Urol 2017;198:810–6.

EUROPEAN UROLOGY 78 (2020) 603–614

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised, Placebo-controlled, Phase 3 Study

Arnulf Stenzl[a,*], *Curtis Dunshee*[b], *Ugo De Giorgi*[c], *Boris Alekseev*[d], *Taro Iguchi*[e], *Russell Z. Szmulewitz*[f], *Thomas W. Flaig*[g], *Bertrand Tombal*[h], *Robert Morlock*[i], *Cristina Ivanescu*[j], *Krishnan Ramaswamy*[k], *Fred Saad*[l], *Andrew J. Armstrong*[m]

[a] *Department of Urology, University Hospital, Eberhard Karls University of Tübingen, Tübingen, Germany;* [b] *Urological Associates of Southern Arizona, Tucson, AZ, USA;* [c] *Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRST IRCCS, Meldola, Italy;* [d] *Herzen Moscow Cancer Research Institute, Moscow, Russia;* [e] *Department of Urology, Osaka City University Graduate School of Medicine, Osaka, Japan;* [f] *Department of Medicine, The University of Chicago, Chicago, IL, USA;* [g] *Division of Medical Oncology, School of Medicine, University of Colorado, Aurora, CO, USA;* [h] *Department of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium;* [i] *Astellas Pharma Inc., Northbrook, IL, USA;* [j] *IQVIA, Amsterdam-Zuidoost, The Netherlands;* [k] *Global HEOR, Pfizer Inc., New York, NY, USA;* [l] *Centre Hospitalier de l'Université de Montréal, Montréal, Canada;* [m] *Duke Cancer Institute Center for Prostate and Urologic Cancer, Durham, NC, USA*

Article info

Article history:
Accepted March 13, 2020

Associate Editor:
Matthew Cooperberg

Statistical Editor:
Emily Zabor

Keywords:
ARCHES
Enzalutamide
Prostate cancer
Metastatic hormone-sensitive
Patient-reported outcomes
Pain

Abstract

Background: In the ARCHES study in metastatic hormone-sensitive prostate cancer (mHSPC), enzalutamide plus androgen deprivation therapy (ADT) improved radiographic progression-free survival (rPFS) versus ADT alone.
Objective: To evaluate patient-reported outcomes (PROs) to week 73.
Design, setting, and participants: ARCHES (NCT02677896) was a randomised, double-blind, placebo-controlled, phase 3 study in mHSPC patients.
Intervention: Enzalutamide (160 mg/day) plus ADT or placebo plus ADT.
Outcome measurements and statistical analysis: PROs were assessed at baseline, week 13, and every 12 wk until disease progression using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (QLQ-PR25), Functional Assessment of Cancer Therapy-Prostate (FACT-P), Brief Pain Inventory Short Form, and EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) instruments. Endpoints included time to first (TTFD) and first confirmed (TTFCD) clinically meaningful deterioration (using predefined questionnaire thresholds) in health-related quality of life (HRQoL) and pain.
Results and limitations: A total of 1150 patients received ADT plus enzalutamide ($n = 574$) or placebo ($n = 576$). Baseline PRO scores indicated high HRQoL and low pain, which was generally maintained in both groups. There were no statistically significant (nominal $p > 0.05$) between-group differences that occurred in both TTFD and TTFCD together for QLQ-PR25 and FACT-P scores. Enzalutamide significantly delayed TTFD in worst pain (by ~3 mo; nominal $p = 0.032$), pain severity (nominal $p = 0.021$), and EQ-5D-5 L visual analogue scale score (nominal $p = 0.0070$) versus placebo (not significant for confirmed deterioration for pain outcomes). Enzalutamide delays deterioration in several HRQoL subscales and pain severity in high-volume disease.

* Corresponding author. Department of Urology, University Hospital, Eberhard Karls University of Tübingen, Hoppe-Seyler Strasse 3, Tübingen, Germany. Tel. +49 707 12986000.
E-mail address: arnulf.stenzl@med.uni-tuebingen.de (A. Stenzl).

https://doi.org/10.1016/j.eururo.2020.03.019

Conclusions: Enzalutamide plus ADT enables men with mHSPC to maintain high-functioning HRQoL and low symptom burden.
Patient summary: This study examined the effect on health-related quality of life and pain of adding enzalutamide or placebo to androgen deprivation therapy for patients with metastatic hormone-sensitive prostate cancer. Addition of enzalutamide allowed patients to maintain their health-related quality of life.

1. Introduction

Enzalutamide is an oral androgen receptor inhibitor approved in Europe and the USA for the treatment of metastatic/nonmetastatic castration-resistant prostate cancer (CRPC) [1,2]. Enzalutamide improves overall survival (OS) in metastatic CRPC and metastasis-free survival in nonmetastatic CRPC, and improves health-related quality of life (HRQoL) [3–5]. In phase 3 trials among men with metastatic hormone-sensitive prostate cancer (mHSPC; also sometimes described as metastatic castration-sensitive prostate cancer) receiving androgen deprivation therapy (ADT), enzalutamide significantly prolonged OS in the ENZAMET trial [6] and radiographic progression-free survival (rPFS) in the ARCHES trial [7]. Since treatment may continue for years, it is critical to examine the impact of more intensive therapy on HRQoL, which may be impaired by disease burden and treatment [8]. Here we report patient-reported outcomes (PROs) from ARCHES.

2. Patients and methods

2.1. Study design and participants

ARCHES (NCT02677896) was a multinational, phase 3, randomised, double-blind, placebo-controlled study in 1150 patients with mHSPC [7]. Eligible men (≥18 yr) had histologically or cytologically confirmed adenocarcinoma of the prostate and metastatic disease.

Eligible patients were randomised centrally (1:1) to ADT (luteinising hormone–releasing hormone agonist/previous bilateral orchiectomy) plus enzalutamide 160 mg daily or matching placebo (each as four capsules orally) until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Patients were allowed up to six cycles of prior docetaxel, ≤3 mo of ADT (≤6 mo if they had received prior docetaxel), or prior neoadjuvant/adjuvant ADT for <39 mo (>9 mo before randomisation). Prespecified stratification factors were disease volume (high vs low; Table 1) and prior docetaxel therapy for prostate cancer (0, 1–5, or 6 cycles).

All patients provided written informed consent compliant with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice, and local regulations. Independent ethics committees or institutional review boards reviewed the ethical, scientific, and medical appropriateness before study commencement.

2.2. Procedures

PROs were assessed at baseline, week 13, and every 12 wk until disease progression. PRO analyses are reported up to week 73 to minimise the impact of missing data given that the median rPFS for placebo plus ADT was 20 mo. After treatment discontinuation, patients underwent long-term follow-up, including monitoring for survival, new antineoplastic therapies for prostate cancer, and symptomatic skeletal events. Patients were scanned every 12 wk and PROs were measured (for those continuing with radiological assessments, if seen in clinic) until confirmed radiographic progression (independent central review) or predefined radiographic progression events (≥262) were reached.

2.3. Outcomes

PRO instruments used (Supplementary Table 1) were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) [9]; Functional Assessment of Cancer Therapy-Prostate (FACT-P) [10]; Brief Pain Inventory Short Form (BPI-SF) [11]; and EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) [12].

The primary endpoint in ARCHES was rPFS. Prespecified secondary PRO endpoints reported here are time to first, or first confirmed, clinically meaningful symptom worsening/HRQoL deterioration (Table 1). Generic terms “time to first clinically meaningful deterioration” (TTFD) and “time to first confirmed clinically meaningful deterioration” (TTFCD) were used for symptom worsening/HRQoL deterioration, with their specific meaning depending on the domain analysed; TTFD in modified urinary symptoms was a key secondary endpoint. Clinically meaningful within-patient change thresholds for FACT-P, BPI-SF, and EQ-5D-5 L were based on previously established values [11,13–17]. In the absence of established thresholds, QLQ-PR25 values were derived using distribution-based and anchor-based analyses. Death was not included in the definition of clinically meaningful deterioration; those who died without deterioration were censored at the last completed assessment. Sensitivity analyses were conducted, including death (from any cause) in the definition. Although no fatigue-specific questionnaire was included, data for FACT-P items assessing lack of energy (GP1) and forced to spend time in bed (GP7) were collected and are presented as exploratory analyses.

Table 1 – Definitions of study endpoints, analyses, and variables.

Endpoint/analysis/ variable	Definition
High-volume disease	High-volume disease consisted of visceral metastases or ≥4 bone lesions (≥1 outside the vertebral column and pelvic bone)
Time to first clinically meaningful deterioration (TTFD)	Time from randomisation to first deterioration in PRO score ≥1 threshold unit that connotes clinically meaningful change to patients vs baseline. Patients with no clinically meaningful deterioration before the end of follow-up, radiographic progression, or death (if not progressed before death) were censored at the last available PRO assessment (date of last non-missing value).
Time to first confirmed clinically meaningful deterioration (TTFCD)	Time from randomisation to first deterioration in PRO score ≥1 threshold unit that connotes clinically meaningful change to patients vs baseline that is confirmed at the next consecutive visit or followed by drop out, resulting in monotone missing data. Patients with no confirmed clinically meaningful deterioration before the end of follow-up, radiographic progression, or death (if not progressed before death) were censored at the last available PRO assessment (date of last non-missing value).
Kaplan-Meier product limit method to estimate distributions of TTFD and TTFCD	TTFD and TTFCD were assessed using Kaplan-Meier estimates. A stratified log-rank test was used to compare these time-to-event variables between treatment groups, adjusting for randomisation stratification factors: volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (yes vs no).
Hazard ratios	Hazard ratios (enzalutamide + ADT/placebo + ADT) and 95% confidence intervals were determined using a stratified Cox proportional-hazards model with treatment as the only covariate and the same randomisation factors (volume of disease score and prior docetaxel therapy for prostate cancer) as strata.
Intent-to-treat population	All patients randomly assigned to study treatment
Observed data	Data collected at each time point without carrying forward previous values
Study size calculation	Study size calculation, based on estimates related to the primary endpoint, was not specifically powered for secondary PRO endpoints; 631 deterioration events would provide 80% power to detect a target hazard ratio of 0.80 based on a two-sided log-rank test and a significance level of 0.05.
Mixed model for repeated measures (MMRM) analyses	An MMRM analysis was used to estimate longitudinal changes in PRO scores from baseline at each scheduled visit.
	MMRM analyses use all available data and assume missing observations are missing at random.
	The dependent variable was change in PRO score from baseline, and the fixed effects were treatment, study visit, and randomisation factors (disease volume and prior docetaxel therapy for prostate cancer) as categorical parameters, baseline PRO score as a continuous parameter, and the interactions between visit and treatment and between baseline PRO score and visit. We used an unstructured variance-covariance matrix to model the covariance structure among each participant's repeated measures. We treated time as a categorical variable so that no restriction is imposed on the trajectory of the means over time. Thus, we estimated and tested the treatment difference in terms of mean change from baseline to a given time point using this MMRM model. The prespecified MMRM analysis was limited to the first 73 weeks after baseline because of the small sample size in both groups beyond this point (<10% of subjects with available data beyond week 73).
Baseline covariates	PRO score, disease volume (low vs high), and prior docetaxel therapy for prostate cancer (yes vs no)
Median follow-up	Median follow-up time in the study for all 1150 patients as determined for the overall survival endpoint. Time is from randomisation up to the date of death or, for those still alive, up to their last known alive date before the analysis cutoff date.

PRO = patient-reported outcome.

2.4. *Statistical analysis*

Study size calculations are shown in Table 1. PRO analyses were performed on the intent-to-treat population and based on observed data (definitions in Table 1). The instrument completion rate (adjusted for study attrition) at each visit was reported for subjects expected to have PRO assessments.

The mean questionnaire score is reported by visit. To estimate longitudinal changes in PRO scores from baseline at each visit, we used a mixed model for repeated measures (MMRM) analysis [18,19] (Table 1). Only patients with baseline and at least one post-baseline score were included in longitudinal change analyses.

The Kaplan-Meier product limit method was used to estimate TTFD and TTFCD distributions, and hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using a stratified Cox proportional-hazards model (Table 1).

For PROs, the proportions of patients with improvement, no change, or deterioration (using the thresholds in Supplementary Table 1) at each visit were compared between groups using a stratified Cochran-Mantel-Haenszel mean score test.

Exploratory subgroup analyses (MMRM, TTFD, and TTFCD) were conducted for prespecified stratification factors and other subgroups. Analyses for disease volume are presented here; other ongoing subgroup analyses will be reported at a later date. Owing to the high volume of data in this paper, we plan to present results for the stratification analysis by prior docetaxel use in a future publication.

We estimated two-sided nominal p values for the PRO analyses (significance testing was set at 0.05) and made no adjustment for multiple testing. Data processing, summarisation, and analyses were performed using SAS v.9.3 (SAS Institute, NC, USA) or higher. The data cutoff date was October 14, 2018.

3. Results

Between March 21, 2016 and January 12, 2018, 1150 patients from 202 centres in 24 countries were randomised to ADT plus either enzalutamide (n = 574) or placebo (n = 576) and included in the intent-to-treat population. At data cutoff (October 14, 2018), the median follow-up (defined in Table 1) for the entire study population was 14.4 mo.

Baseline demographics and PRO scores were well balanced between the groups. The majority of patients had high-volume disease and no prior docetaxel therapy for

Table 2 – Change in least-squares mean for PRO scores at week 73 (mixed-model for repeated measures).

Instrument[a]	Least-squares mean (SE)		TD at week 73
	ENZA + ADT	PBO + ADT	(95% CI)
EORTC QLQ-PR25 scores[b]			
Modified urinary symptoms	−2.22 (1.84)	−1.18 (2.01)	−1.04 (−6.20, 4.11)
Urinary symptoms	−0.56 (1.30)	−0.02 (1.42)	−0.54 (−4.19, 3.11)
Bowel symptoms/function	0.92 (0.73)	0.59 (0.79)	0.33 (−1.72, 2.38)
Treatment-related symptoms	7.08 (1.00)	4.61 (1.09)	2.46 (−0.35, 5.27)
Incontinence aids[c]	−4.08 (3.22)	3.99 (3.04)	−8.07 (−16.44, 0.30)
Sexual functioning	−3.07 (4.91)	−16.67 (9.30)	13.59 (−7.86, 35.1)
Sexual activity	−2.45 (1.61)	−4.87 (1.74)	2.42 (−2.12, 6.95)
FACT scores[c]			
FACT-P total	−3.17 (1.30)	−1.71 (1.42)	−1.47 (−5.12, 2.18)
Physical wellbeing	−1.42 (0.32)	−0.40 (0.34)	−1.02 (−1.90, −0.13)*
Functional wellbeing	−0.41 (0.40)	−0.15 (0.43)	−0.26 (−1.37, 0.85)
Emotional wellbeing	−0.30 (0.28)	0.06 (0.31)	−0.36 (−1.16, 0.44)
Social wellbeing	0.47 (0.35)	−0.37 (0.38)	0.84 (−0.12, 1.80)
Prostate cancer subscale	−1.01 (0.47)	−0.50 (0.52)	−0.51 (−1.84, 0.81)
Prostate cancer subscale-pain	−1.01 (0.29)	−0.56 (0.32)	−0.45 (−1.29, 0.38)
FACT Advanced Prostate Symptom Index	−0.77 (0.37)	−0.01 (0.40)	−0.76 (−1.79, 0.27)
Trial outcome index	−3.15 (0.98)	−1.28 (1.07)	−1.88 (−4.62, 0.87)
FACT-General	−1.94 (0.95)	−1.08 (1.04)	−0.86 (−3.54, 1.82)
BPI-SF scores[b]			
Worst pain (item 3)	0.54 (0.19)	0.33 (0.20)	0.21 (−0.32, 0.73)
Severity	0.49 (0.15)	0.38 (0.16)	0.11 (−0.30, 0.52)
Interference	0.71 (0.15)	0.58 (0.17)	0.14 (−0.29, 0.57)
EQ-5D-5 L scores[c]			
Visual analogue scale	0.28 (1.16)	0.19 (1.27)	0.10 (−3.14, 3.33)

ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory Short Form; CI = confidence interval; ENZA = enzalutamide; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5 L = EuroQoL 5-Dimensions, 5-Levels; FACT = Functional Assessment of Cancer Therapy; FACT-P = FACT-Prostate; PBO = placebo; PRO = patient-reported outcome; SE = standard error; TD = treatment difference for ENZA versus PBO.

* $p = 0.024$ from the mixed-model repeated measures analyses.

[a] For BPI-SF scores and EORTC QLQ-PR25 bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms scores, a positive change from baseline value indicates worsening of symptoms. For FACT-P scores and EQ-VAS, a positive change from baseline value indicates improvement. Therefore, a negative number for the least-squares mean difference at week 73 favours ENZA + ADT over PBO + ADT for BPI-SF scores and bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms and problems, whereas a positive number favours ENZA + ADT over PBO + ADT for FACT-P scores and EQ-VAS.

[b] A positive change from baseline indicates worsening of symptoms.

[c] A positive change from baseline indicates improvement of symptoms.

prostate cancer. Baseline PRO scores suggest that patients were generally asymptomatic with good HRQoL, low symptom burden, and minimal functional limitations (Supplementary Table 2).

Pain was low at baseline; approximately half (48%) of patients (similar in both groups) reported a worst pain score of 0 ("no pain"). For PRO outcomes, all questions were completed at baseline by 94–96% of patients on enzalutamide versus 95–96% of patients on placebo. At week 73, completion rates (all questions completed), based on patients remaining on study and available for assessment, ranged from 87% to 88% (Supplementary Fig. 1).

Mean scores by visit indicated that high levels of HRQoL and low levels of pain at baseline were generally maintained during the study in both groups (Supplementary Fig. 2). There were no statistically significant or clinically meaningful differences between the groups in mean change in PRO score from baseline to week 73, except for a statistically significant (nominal $p = 0.024$) difference in FACT-P physical wellbeing score favouring placebo over enzalutamide, although the difference was not clinically meaningful (Table 2). The proportion of patients with clinically meaningful deterioration in modified urinary symptoms, FACT-P total, BPI-SF worst pain, and EQ-5D-5 L visual analogue scale (VAS) scores over time was generally low and similar between the groups (Fig. 1); this also applied to other PRO domains (Supplementary Figs. 3–5). Although higher proportions of patients reported deterioration in sexual functioning over time (Supplementary Fig. 3D), which was higher with placebo versus enzalutamide, patient numbers were very small.

There were no statistically significant (nominal $p > 0.05$) differences in median time to clinically meaningful deterioration (that occurred in both TTFD and TTFCD together) between treatments for QLQ-PR25 (Fig. 2A) or FACT-P (Fig. 2B) domain scores. Enzalutamide plus ADT significantly delayed TTFD in worst pain (14.09 vs 11.10 mo; HR 0.82; nominal $p = 0.032$) and pain severity (19.38 vs 16.76 mo; HR 0.79; nominal $p = 0.021$) versus placebo plus ADT (Fig. 2C). There was no significant between-treatment difference in time to deterioration for pain interference or with TTFCD for worst pain and pain severity. The median time to deterioration on EQ-5D-5 L VAS was significantly delayed with enzalutamide plus ADT versus placebo plus ADT (TTFD 11.14 vs 8.38 mo; HR 0.80, 95% CI 0.67–0.94; nominal $p = 0.0070$). TTFCD for EQ-5D-5 L VAS still showed a

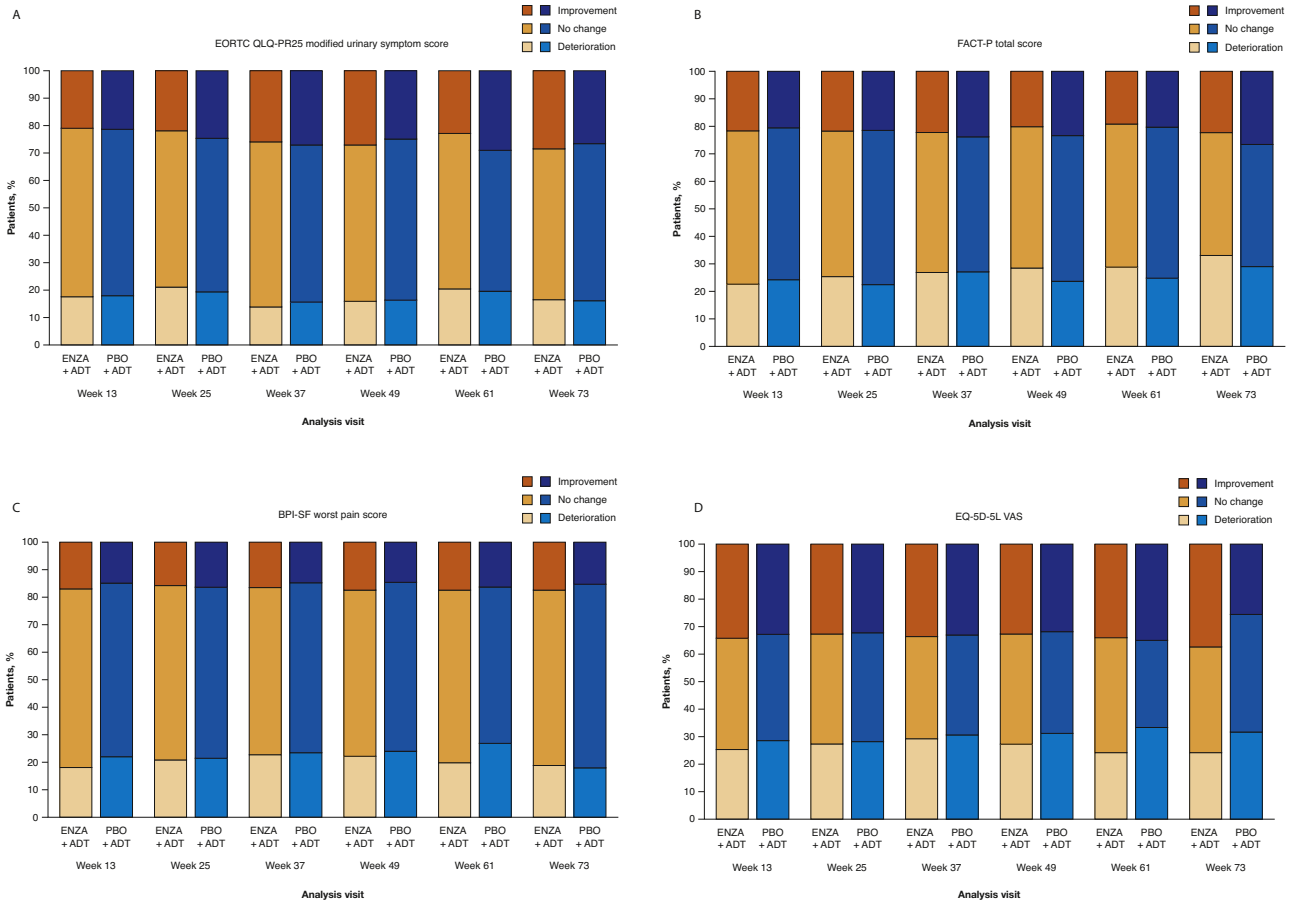


Fig. 1 – Proportion of patients with clinically meaningful improvement, no change, or deterioration from baseline for (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25) modified urinary symptom score, (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score, (C) Brief Pain Inventory Short Form (BPI-SF) worst pain score, and (D) EuroQoL 5-Dimensions, 5-Levels (EQ-5D-5 L) visual analogue scale (VAS) over time to week 73. Nominal $p > 0.05$ for enzalutamide versus placebo at each time point. ADT = androgen deprivation therapy; ENZA = enzalutamide; PBO = placebo.

significant between-group difference in favour of enzalutamide. Sensitivity analyses including death in the definition showed similar results (Supplementary Table 3).

PROs were analysed by disease volume at baseline according to criteria from the CHAARTED trial. The median time to deterioration (that occurred in both TTFD and TTFCD together) was significantly delayed with enzalutamide versus placebo for FACT-P total (TTFD HR 0.78; nominal $p = 0.020$; TTFCD HR 0.74; nominal $p = 0.012$), FACT-P social wellbeing (TTFD HR 0.79; nominal $p = 0.035$; TTFCD HR 0.74; nominal $p = 0.025$), and TTFCD only was also delayed for worst pain (TTFCD not yet reached vs 17.22 mo; HR 0.75; nominal $p = 0.030$) in high-volume disease (Fig. 3). Deterioration on EQ-5D-5 L VAS was also significantly delayed with enzalutamide versus placebo (TTFD 11.27 vs 8.34 mo; HR 0.77, 95% CI 0.62–0.94; nominal $p = 0.012$; TTFCD 16.76 vs 13.73 mo; HR 0.72, 95% CI 0.57-0.91; nominal $p = 0.0064$) in high-volume disease. Further subgroup analyses showed no statistically significant or clinically meaningful between-group differences in change in mean PRO scores from baseline to week 73 for low- or high-volume disease, except for a statistically significant (nominal $p = 0.037$) difference in FACT-P physical wellbeing score favouring placebo over enzalutamide in low-volume disease (difference not clinically meaningful at predefined threshold; Supplementary Table 4).

Among men with low-volume mHSPC, there was a delay in time to first deterioration with placebo versus enzalutamide for some measures, but not in confirmed deterioration for FACT-P total (TTFD HR 1.41; nominal $p = 0.020$; TTFCD HR 1.31; nominal $p = 0.11$), prostate cancer subscale (TTFD HR 1.38; nominal $p = 0.013$; TTFCD HR 1.21; nominal $p = 0.2$), and trial outcome index (TTFD HR 1.46; nominal $p = 0.011$; TTFCD HR 1.36; nominal $p = 0.077$; Fig. 3). Only a minority of patients were sexually active; time to deterioration in sexual activity was longer in the placebo group than in the enzalutamide group (TTFD HR 1.50; nominal $p = 0.051$; TTFCD HR 1.58; nominal $p = 0.045$).

The proportions of patients with worsening ($\geq$1 point) lack of energy from baseline to week 73 for enzalutamide and placebo were 39–48% and 26–41% in low-volume disease, and 27–36% and 24–29% in high-volume disease, respectively (Supplementary Table 5). Patients reporting spending a longer time in bed for enzalutamide and placebo were 9.4–15% and 4.3–15% in low-volume disease, and 12–16% and 13–18% in high-volume disease, respectively

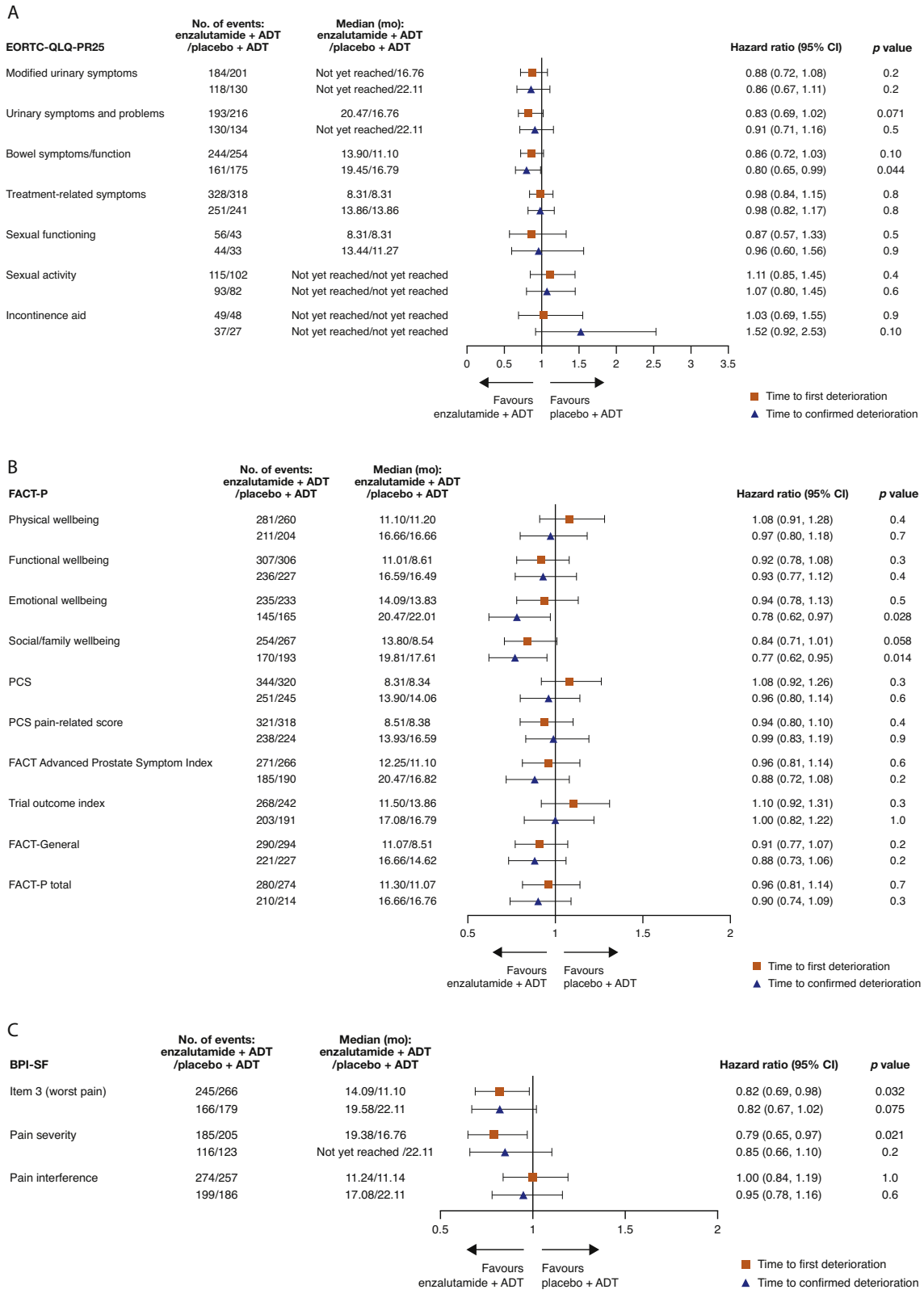
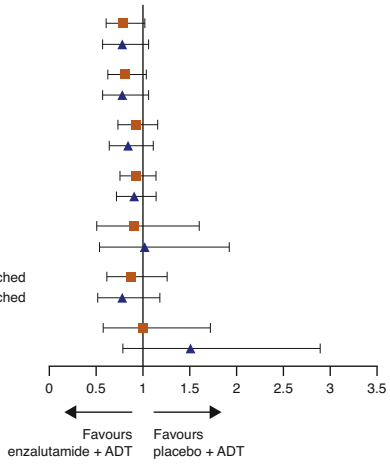


Fig. 2 – Time to first clinically meaningful deterioration and time to first confirmed clinically meaningful deterioration in (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC-QLQ-PR25), (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P), and (C) Brief Pain Inventory Short Form (BPI-SF) scores. Thresholds for minimum clinically meaningful deterioration in scores from baseline were 3 points for physical wellbeing, functional wellbeing, emotional wellbeing, family/social wellbeing, PCS, and FACT Advanced Prostate Symptom Index; 2 points for PCS pain-related score; 9 points for trial outcome index; 7 points for FACT-General; and 10 points for FACT-P. Pain progression was defined as a ≥2-point increase in BPI-SF pain score from baseline (except for pain interference, ≥1). ADT = androgen deprivation therapy; CI = confidence interval; PCS = prostate cancer subscale.

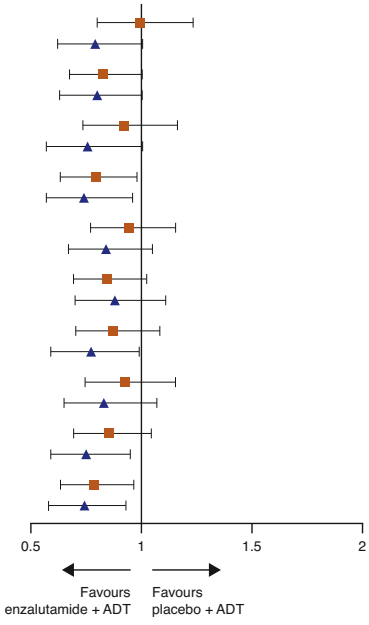
A

EORTC-QLQ-PR25	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Modified urinary symptoms	106/130	Not yet reached/16.76	0.79 (0.61, 1.02)	0.076
	72/88	Not yet reached/19.38	0.78 (0.57, 1.06)	0.12
Urinary symptoms and problems	113/134	20.47/16.79	0.81 (0.63, 1.04)	0.099
	76/92	Not yet reached/22.11	0.78 (0.57, 1.06)	0.11
Bowel symptoms/function	151/151	13.93/11.14	0.93 (0.74, 1.16)	0.5
	102/105	19.45/16.79	0.84 (0.64, 1.11)	0.2
Treatment-related symptoms	196/202	8.31/8.31	0.93 (0.76, 1.14)	0.5
	147/153	16.20/13.80	0.91 (0.72, 1.14)	0.4
Sexual functioning	24/27	8.41/11.07	0.90 (0.51, 1.60)	0.7
	19/21	13.44/13.77	1.02 (0.54, 1.92)	1.0
Sexual activity	57/64	Not yet reached/not yet reached	0.88 (0.62, 1.26)	0.5
	42/51	Not yet reached/not yet reached	0.78 (0.52, 1.18)	0.2
Incontinence aid	26/27	19.38/not yet reached	1.00 (0.58, 1.72)	1.0
	22/16	19.38/not yet reached	1.51 (0.79, 2.89)	0.2



B

FACT-P	No. of events: enzalutamide + ADT /placebo + ADT	Median (months): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	p-value
Physical wellbeing	167/169	11.17/11.20	0.99 (0.80, 1.23)	0.9
	121/139	19.32/16.66	0.79 (0.62, 1.01)	0.061
Functional wellbeing	187/202	11.07/8.38	0.82 (0.67, 1.00)	0.055
	142/154	16.59/11.89	0.80 (0.63, 1.00)	0.053
Emotional wellbeing	142/147	16.59/13.83	0.92 (0.73, 1.16)	0.5
	88/106	20.47/22.11	0.76 (0.57, 1.01)	0.057
Social/family wellbeing	151/174	13.86/8.51	0.79 (0.63, 0.98)	0.035
	103/125	19.81/16.79	0.74 (0.57, 0.96)	0.025
PCS	198/209	10.97/8.34	0.94 (0.77, 1.15)	0.5
	148/125	13.93/13.01	0.84 (0.67, 1.05)	0.12
PCS pain-related score	195/213	11.04/8.31	0.84 (0.69, 1.02)	0.080
	147/155	13.93/13.86	0.88 (0.70, 1.11)	0.3
FACT Advanced Prostate Symptom Index	160/175	13.73/11.07	0.87 (0.70, 1.08)	0.2
	109/130	20.47/16.82	0.77 (0.59, 0.99)	0.042
Trial outcome index	155/162	13.83/11.14	0.92 (0.74, 1.15)	0.5
	123/135	17.18/16.59	0.83 (0.65, 1.07)	0.15
FACT-General	174/190	11.10/8.61	0.85 (0.69, 1.04)	0.12
	130/152	16.76/13.86	0.75 (0.59, 0.95)	0.018
FACT-P total	164/191	11.40/8.48	0.78 (0.63, 0.96)	0.020
	125/152	16.69/13.86	0.74 (0.58, 0.93)	0.012



C

BPI-SF	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Item 3 (worst pain)	159/177	13.86/11.01	0.83 (0.67, 1.03)	0.087
	106/127	Not yet reached/17.22	0.75 (0.58, 0.97)	0.030
Pain severity	118/136	19.32/16.59	0.77 (0.60, 0.98)	0.036
	77/89	Not yet reached /22.11	0.78 (0.58, 1.07)	0.12
Pain interference	170/177	11.30/10.22	0.89 (0.72, 1.11)	0.3
	127/129	16.72/16.62	0.89 (0.69, 1.14)	0.3

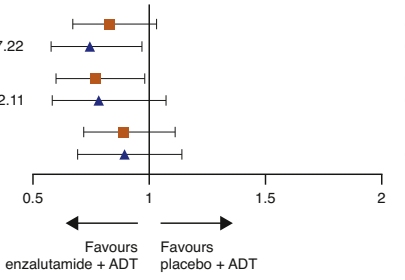
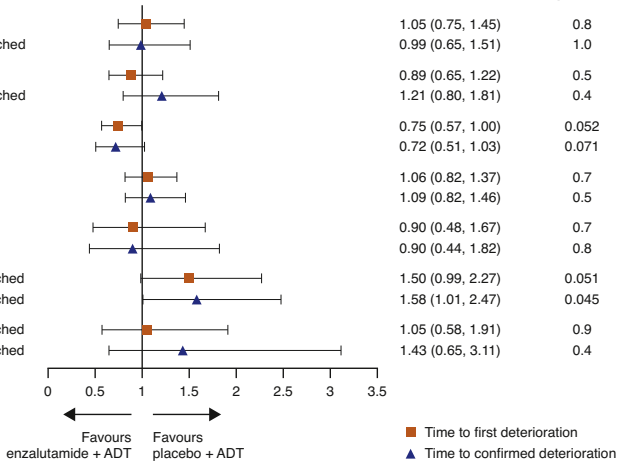


Fig. 3 – Time to first clinically meaningful deterioration and time to first confirmed clinically meaningful deterioration in (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (EORTC-QLQ-PR25), (B) Functional Assessment of Cancer Therapy-Prostate (FACT-P), and (C) Brief Pain Inventory Short Form (BPI-SF) scores among patients with high-volume disease, and in (D) EORTC-QLQ-PR25, (E) FACT-P, and (F) BPI-SF scores among patients with low-volume disease. The threshold for minimum clinically meaningful deterioration in score from baseline was 3 points for physical wellbeing, functional wellbeing, emotional wellbeing, family/social wellbeing, PCS, and FACT Advanced Prostate Symptom Index; 2 points for PCS pain-related score; 9 points for trial outcome index; 7 points for FACT-General; and 10 points for FACT-P. Pain progression was defined as a ≥2-point increase in BPI-SF pain score from baseline (except for pain interference, ≥1). ADT = androgen deprivation therapy; CI = confidence interval; PCS = prostate cancer subscale.

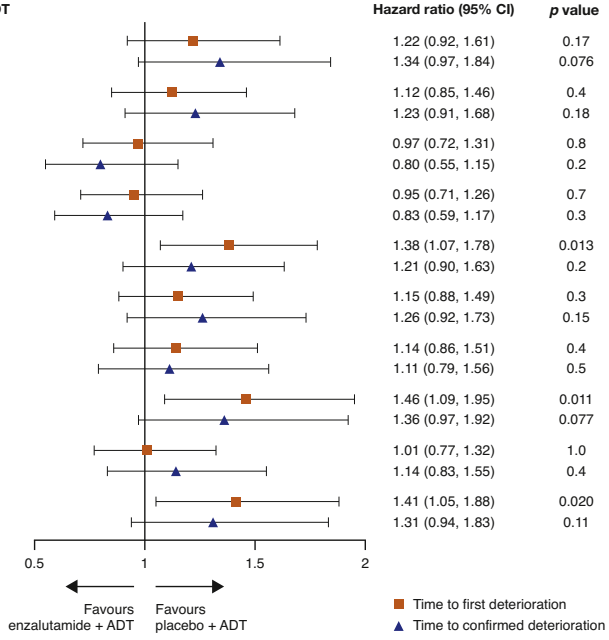
D

EORTC-QLQ-PR25	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Modified urinary symptoms	78/71	Not yet reached/19.25	1.05 (0.75, 1.45)	0.8
	46/42	Not yet reached/Not yet reached	0.99 (0.65, 1.51)	1.0
Urinary symptoms and problems	80/82	19.22/16.69	0.89 (0.65, 1.22)	0.5
	54/42	Not yet reached/Not yet reached	1.21 (0.80, 1.81)	0.4
Bowel symptoms/function	93/103	13.86/10.97	0.75 (0.57, 1.00)	0.052
	59/70	22.31/16.79	0.72 (0.51, 1.03)	0.071
Treatment-related symptoms	132/116	8.18/6.01	1.06 (0.82, 1.37)	0.7
	104/88	13.40/13.93	1.09 (0.82, 1.46)	0.5
Sexual functioning	32/16	5.75/8.31	0.90 (0.48, 1.67)	0.7
	25/12	11.30/11.10	0.90 (0.44, 1.82)	0.8
Sexual activity	58/38	Not yet reached/not yet reached	1.50 (0.99, 2.27)	0.051
	51/31	Not yet reached/not yet reached	1.58 (1.01, 2.47)	0.045
Incontinence aid	23/21	Not yet reached/not yet reached	1.05 (0.58, 1.91)	0.9
	15/11	Not yet reached/not yet reached	1.43 (0.65, 3.11)	0.4



E

FACT-P	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Physical wellbeing	114/91	11.07/13.70	1.22 (0.92, 1.61)	0.17
	90/65	14.09/16.66	1.34 (0.97, 1.84)	0.076
Functional wellbeing	120/104	8.44/11.04	1.12 (0.85, 1.46)	0.4
	94/73	13.90/16.79	1.23 (0.91, 1.68)	0.18
Emotional wellbeing	93/86	13.86/13.83	0.97 (0.72, 1.31)	0.8
	57/59	19.45/22.01	0.80 (0.55, 1.15)	0.2
Social/family wellbeing	103/93	11.17/8.54	0.95 (0.71, 1.26)	0.7
	67/68	22.11/22.11	0.83 (0.59, 1.17)	0.3
PCS	146/111	5.55/8.44	1.38 (1.07, 1.78)	0.013
	103/80	13.86/16.36	1.21 (0.90, 1.63)	0.2
PCS pain-related score	126/105	8.34/11.04	1.15 (0.88, 1.49)	0.3
	91/69	16.59/16.69	1.26 (0.92, 1.73)	0.15
FACT Advanced Prostate Symptom Index	111/91	11.07/13.83	1.14 (0.86, 1.51)	0.4
	76/60	19.22/19.35	1.11 (0.79, 1.56)	0.5
Trial outcome index	113/80	11.07/16.62	1.46 (1.09, 1.95)	0.011
	80/56	16.59/19.35	1.36 (0.97, 1.92)	0.077
FACT-General	116/104	8.84/8.34	1.01 (0.77, 1.32)	1.0
	91/75	16.59/16.69	1.14 (0.83, 1.55)	0.4
FACT-P total	116/83	11.04/16.69	1.41 (1.05, 1.88)	0.020
	85/62	16.59/19.35	1.31 (0.94, 1.83)	0.11



F

BPI-SF	No. of events: enzalutamide + ADT /placebo + ADT	Median (mo): enzalutamide + ADT /placebo + ADT	Hazard ratio (95% CI)	*p* value
Item 3 (worst pain)	86/89	16.59/13.86	0.85 (0.63, 1.15)	0.3
	60/52	19.58/not yet reached	1.03 (0.71, 1.49)	0.9
Pain severity	67/69	Not yet reached/19.25	0.84 (0.60, 1.18)	0.3
	39/34	Not yet reached / not yet reached	1.03 (0.65, 1.63)	0.9
Pain interference	104/80	11.24/17.02	1.24 (0.92, 1.66)	0.16
	72/57	19.42/not yet reached	1.09 (0.77, 1.55)	0.6

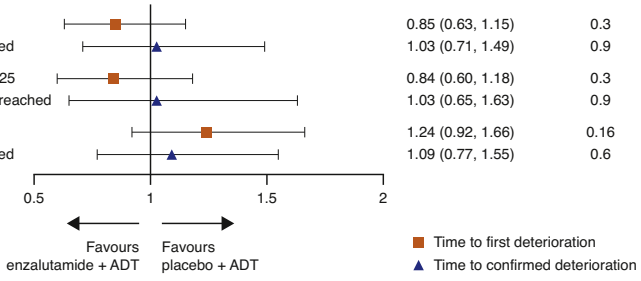
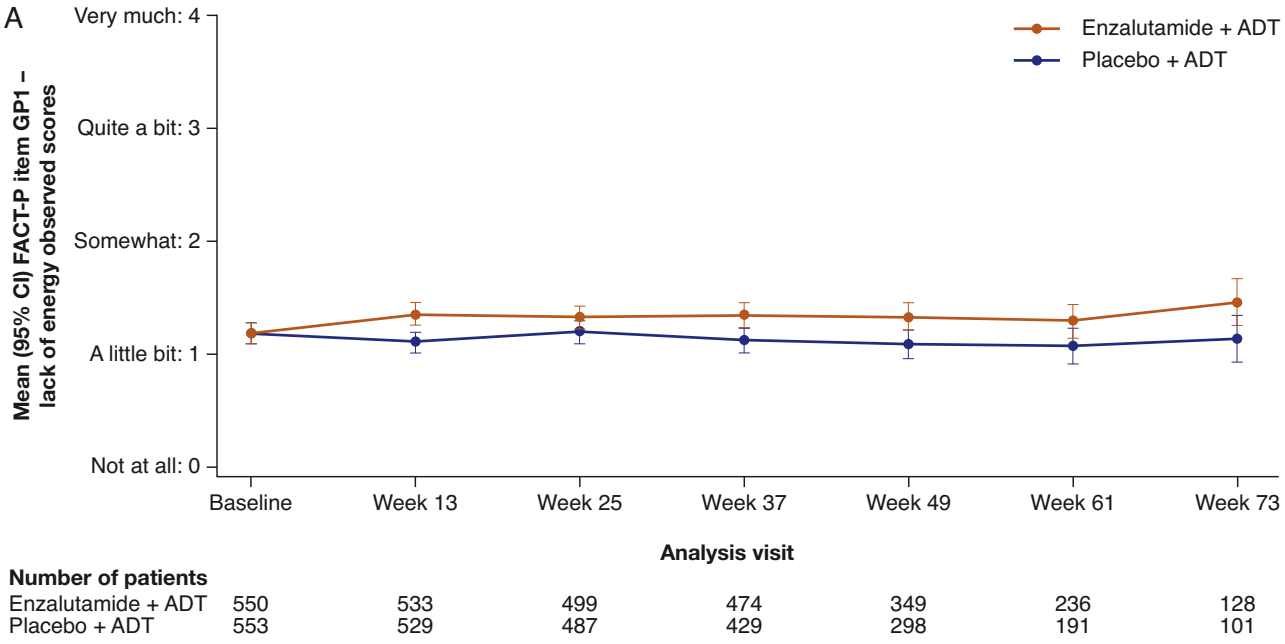


Fig. 3. (*Continued*).



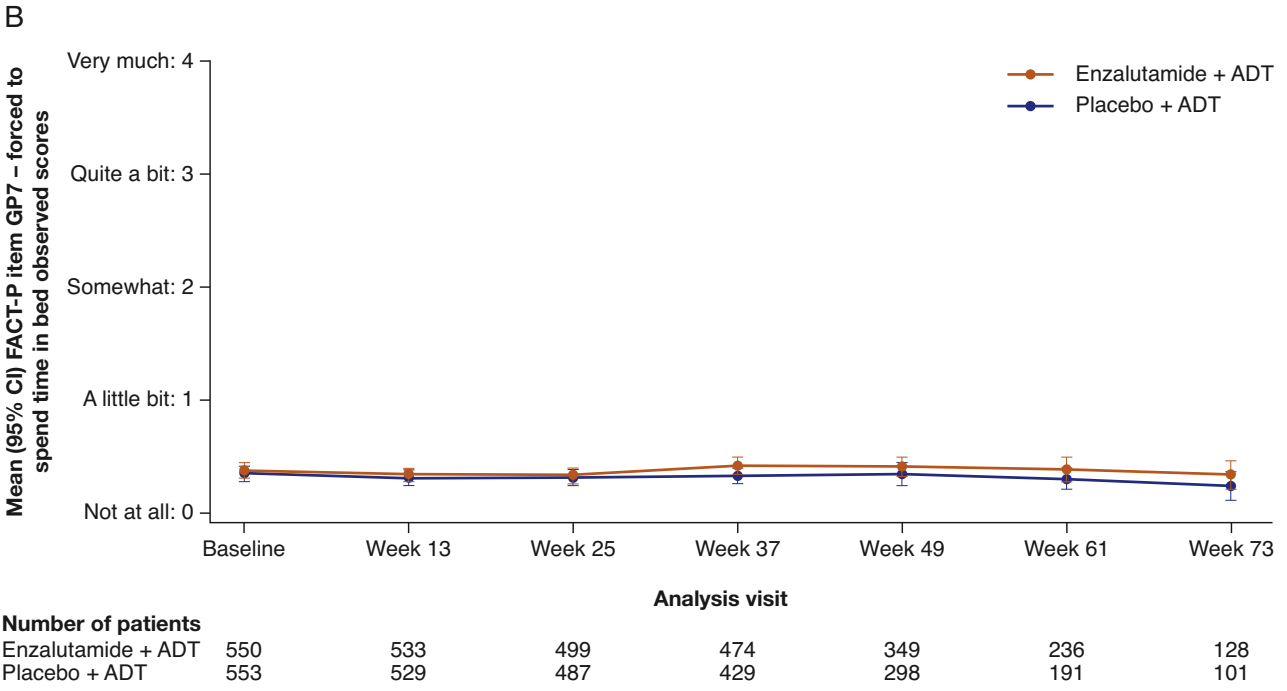


Fig. 4 – Mean scores over time to week 73 for the Functional Assessment of Cancer Therapy-Prostate (FACT-P) items (A) GP1 – lack of energy and (B) GP7 – forced to spend time in bed. ADT = androgen deprivation therapy; CI = confidence interval; PBO = placebo.

(Supplementary Table 6). Mean scores for lack of energy and forced to spend time in bed items (Fig. 4) showed no change over time and were similar between the treatment groups.

4. Discussion

Decisions on the merits of more intensive hormonal therapy in mHSPC should reflect overall net benefits over risks versus ADT alone, including HRQoL. ARCHES demonstrates that high-functioning HRQoL and low symptom burden at baseline are generally maintained post-baseline when enzalutamide is added to ADT. Enzalutamide significantly prolongs time to progression for worst pain and pain severity versus placebo, and significantly delays time to deterioration on EQ-5D-5 L VAS versus placebo for TTFD. There was no difference between treatments in TTFD for other PROs. However, the prespecified confirmed deterioration analysis showed no significant differences between

treatments for worst pain or pain severity. Thus, the data suggest that adding enzalutamide to ADT does not worsen HRQoL and has a beneficial effect on EQ-5D-5 L VAS, but no statistically significant benefit for deterioration of pain versus placebo. Longer follow-up is needed to understand the impact of enzalutamide plus ADT on HRQoL in subsequent years or beyond disease progression. For FACT-P items measuring patient-reported fatigue (lack of energy/forced to spend time in bed), mean values to week 73 were stable and generally similar between the groups.

Subgroup analyses showed a significant delay in deterioration with enzalutamide versus placebo for several HRQoL subscales and pain severity among men with high-volume mHSPC; conversely, in low-volume disease, there was a modest delay in TTFD with placebo plus ADT versus enzalutamide plus ADT for some FACT-P scales. Since enzalutamide was effective regarding rPFS in both high- and low-volume disease, this may simply reflect that patients with low-volume disease are asymptomatic at baseline and are more impacted by hormone-related symptoms; however, the prespecified confirmed deterioration analysis showed no significant differences between the treatment groups for the low-volume population, except for sexual activity favouring placebo. However, the population in this category was small and the results should be interpreted with caution. The confirmed deterioration analysis may be a more accurate measure, as it ensures that scores are consistently reduced and not fluctuating from a deterioration to a non-deterioration score. This indicates that the clinical benefit in both populations does not come at a significant HRQoL cost, although patients with low-volume disease may experience some numerical decrement.

In ARCHES, enzalutamide plus ADT significantly improved rPFS versus ADT alone, irrespective of disease volume and prior docetaxel [7]. In ENZAMET, enzalutamide plus ADT improved OS versus nonsteroidal antiandrogen therapy plus ADT, irrespective of disease volume, and despite the more common use of concurrent docetaxel for men with mHSPC [6]. In ENZAMET, docetaxel could be given concomitantly with enzalutamide, unlike ARCHES, where docetaxel use was before enzalutamide. Critical to an understanding of the net benefits of more intensive therapy is the impact on HRQoL of enzalutamide plus ADT in patients over time. Importantly, in ARCHES, men commenced ADT before study entry, and thus had low prostate-specific antigen (PSA) and good HRQoL on enrolment [7]. This probably explains why men entering ARCHES were generally asymptomatic with low urinary symptom burden, good HRQoL, and low pain. Indeed, baseline PRO scores in ARCHES are generally similar to those in the PROSPER study [5] (Supplementary Table 7) in nonmetastatic prostate cancer and comparable to those in the general population [20].

HRQoL and pain status before ADT were not captured until study entry. Patients could receive ADT for ≤3 mo (6 mo if treated with docetaxel) before study initiation. Thus, it is likely that the effects of ADT on HRQoL were already evident in most patients at enrolment. Pre-randomisation ADT, while associated with adverse effects, can improve lower urinary tract symptoms in all prostate cancer stages [21] and help reduce bone pain in advanced disease [22].

Maintenance of HRQoL in ARCHES adds to the efficacy benefits of enzalutamide plus ADT in mHSPC, including significantly improved rPFS, time to PSA progression, time to initiation of new antineoplastic therapy, and time to first symptomatic skeletal event versus placebo plus ADT [7]. Improvements in PROs, in addition to survival, also occur with enzalutamide in CRPC [3–5].

Our results are in agreement with those from studies comparing abiraterone acetate and prednisone plus ADT [23], docetaxel plus ADT, and apalutamide plus ADT [24] versus ADT alone [25] in mHSPC. Patients in both the LATITUDE and CHAARTED studies appeared to show good HRQoL at baseline [23,25]. In LATITUDE, comprising patients with newly diagnosed (≤3 mo pre-randomisation) mHSPC, addition of abiraterone acetate and prednisone to ADT significantly prolonged time to worst pain intensity progression and improved health status (measured with EQ-5D-5 L) versus ADT alone [23]. However, differences between populations and study designs make direct comparisons difficult. Unlike ARCHES, LATITUDE comprised a high-risk population, with higher proportions of patients with Eastern Cooperative Oncology Group score ≥1, Gleason score ≥8, and distant metastases. Baseline BPI-SF pain scores also appeared to be generally higher (indicating greater pain) in LATITUDE [23]. Furthermore, in the ARCHES and CHAARTED studies, assessments were conducted every 12 wk versus every 4 wk in LATITUDE for the first 13 mo, followed by every 8 wk. In CHAARTED, FACT-P total scores were significantly lower after 3 mo of docetaxel plus ADT versus ADT alone, and were not improved until 12 mo, perhaps reflecting reversible short-term physical and functional deficits at 3 mo, presumably associated with chemotherapy. Unlike ARCHES, patients were not blinded and knowledge of having received chemotherapy may have influenced HRQoL reporting [25].

We used clinically meaningful HRQoL change thresholds from the literature to interpret FACT-P, BPI-SF, and EQ-5D-5 L scores. Cutoff values of ≥30% or a ≥2-point change in BPI-SF scores have been proposed for detection of clinically important improvements in studies of cancer-related breakthrough pain and chronic pain states [15,16] and in metastatic CRPC [3,26]. However, use of these values in defining pain progression in patients with mHSPC is not yet validated. In view of the very low baseline pain scores in our study, we applied fixed thresholds of ≥1 point (interference) or ≥2 points (worst pain/pain severity), as these are likely to be more meaningful changes from baseline than 30–50% changes, which would have been very small [26]. No threshold values have been established for QLQ-PR25. We therefore derived thresholds using distribution-based and anchor-based analyses; derivation of correlation coefficients between anchors and QLQ-PR25 scores showed that the anchors are adequate.

Study limitations include patient selection using specific criteria, so the results might not be generalisable to other disease-stage prostate cancer populations. There was an absence of HRQoL data before ADT initiation and limited data after treatment discontinuation. This limited our

ability to document improved HRQoL with initial ADT before enzalutamide, and missing HRQoL data over time is a well-established drawback of studies incorporating PROs as secondary or exploratory endpoints [3]. This pattern of attrition makes data interpretation difficult and can lead to overestimation of HRQoL at later time points. To address this imbalance, MMRM analysis of longitudinal data is limited to 73 weeks. Finally, the follow-up duration in ARCHES is short. Given the positive efficacy results with enzalutamide plus ADT in ARCHES and survival benefits in ENZAMET [6], patients are now being offered access to enzalutamide plus ADT in this setting, which will limit our ability to observe HRQoL differences over time between treatments. Study strengths include the randomised and prospective design, high rates of instrument compliance, and high regional/ethnic diversity of the population.

In conclusion, men with mHSPC are generally asymptomatic, with high levels of HRQoL and low levels of pain at baseline. Notably, the effects of ongoing ADT on HRQoL were already experienced by most patients by study enrolment. Prolongation of rPFS with enzalutamide plus ADT is accompanied by maintenance of HRQoL. Thus, enzalutamide represents a treatment strategy for mHSPC that provides clinical benefits while maintaining HRQoL.

Author contributions: Arnulf Stenzl had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ramaswamy, Armstrong.
Acquisition of data: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Flaig, Armstrong.
Analysis and interpretation of data: Stenzl, Alekseev, Iguchi, Szmulewitz, Flaig, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
Drafting of the manuscript: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Szmulewitz, Flaig, Tombal, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
Critical revision of the manuscript for important intellectual content: Stenzl, Dunshee, De Giorgi, Alekseev, Iguchi, Szmulewitz, Flaig, Tombal, Morlock, Ivanescu, Ramaswamy, Saad, Armstrong.
Statistical analysis: Ivanescu, Ramaswamy.
Obtaining funding: None.
Administrative, technical, or material support: None
Supervision: None.
Other: None.

Financial disclosures: Arnulf Stenzl certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Arnulf Stenzl reports research funding from Astellas and Medivation during the conduct of the study; consultant/advisory role, research funding, and travel/accommodation/expenses from Ipsen Pharma and Janssen; consultant/advisory role from Roche, Alere, BMS, and Stebatiotechnology; travel/accommodation/expenses from Ferring, CureVac, and Sanofi Aventis; research funding from Karl Storz AG and AstraZeneca; and expert testimony on photodynamic therapy for prostate cancer from GBA outside the submitted work. He also reports patents pending: A290/99 (implanted incontinence device); AT00/0001 (C-Trap, implantable device to treat urinary incontinence); and 2018/6579 (gene expression signature for subtype and prognostic prediction of renal cell carcinoma). Curtis Dunshee reports consulting/advisory role and research funding from Astellas and consulting/advisory role for Pfizer during the conduct of the study, and research funding from Churchill Pharmaceuticals, Medivation, Janssen Oncology, Dendreon, Ferring, BHR Pharma, Eleven Biotherapeutics, Myovant Sciences, Siemens, AstraZeneca, Exact Sciences, and Teso RX Pharmaceuticals outside the submitted work. Ugo De Giorgi reports consulting/advisory role for Astellas and consulting/advisory role, travel, and accommodation from Pfizer during the conduct of the study; consulting/advisory role, speakers bureau, research funding, and travel accommodation/expenses from AstraZeneca; consulting/advisory role, travel, and accommodation from Janssen, Bristol-Myers Squibb, and Ipsen; consulting/advisory role and research funding from Sanofi; consulting/advisory role for Bayer and Merck; and research funding from Roche outside the submitted work. Boris Alekseev reports consulting/advisory role, speakers bureau, research funding, and travel accommodation/expenses from Astellas and Pfizer during the conduct of the study; consulting/advisory role, speakers bureau, research funding, and travel accommodation/expenses from AstraZeneca, Bayer, BMS, Janssen, and MSD; and consulting/advisory role, speakers' bureau, and travel accommodation/expenses from Ferring and Sanofi outside the submitted work. Taro Iguchi reports consulting/advisory role, speakers bureau, and research funding from Astellas during the conduct of the study; and consulting/advisory role, speakers bureau, and research funding from Bayer; consulting/advisory role and speakers bureau from Janssen; and speakers bureau from Sanofi, outside the submitted work. Russell Z. Szmulewitz reports consulting/advisory role and research funding from Astellas and consulting/advisory role for Pfizer during the conduct of the study; and research funding, consulting/advisory role for Abbvie and Janssen Oncology; research funding from Incyte and Macrogenics; consulting/advisory role for AstraZeneca, Merck, Amgen, Sanofi, and Exelixis; and travel/accommodation/expenses from Corcept Therapeutics outside the submitted work. He also reports a patent for AR/GR inhibition in prostate cancer licensed to Corcept Therapeutics (Patent licensed by University of Chicago of which Russell Z. Szmulewitz is co-inventor to Corcept Therapeutics AR/GR inhibition in prostate cancer). Thomas W. Flaig reports consulting/advisory role and research funding from Astellas and research funding from Pfizer during the conduct of the study; leadership role and stock from Aurora Oncology; personal fees/honoraria from BN Immuno Therapeutics; consultant/advisory role and research funding from GTX; and research funding from Novartis, Bavarian Nordic, Dendreon, Janssen Oncology, Medivation, Sanofi, Bristol-Myers Squibb, Roche/Genentech, Exelixis, Aragon Pharmaceuticals, Sotio, Tokai Pharmaceuticals, MedImmune, Lilly, Agensys, Seattle Genetics, La Roche-Posay, and Merck outside the submitted work. Bertrand Tombal reports personal fees and consultancy, advisory board, honoraria, and speakers bureau fees from Astellas during the conduct of the study; and personal fees/honoraria from Bayer, Janssen, and Sanofi, and personal fees/consulting/advisory role for Amgen, Ipsen, and Takeda outside the submitted work. Robert Morlock reports personal fees from Astellas during the conduct of the study; and personal fees/consulting or advisory role from Abbot Medical Optics, Ironwood, and Genentech, outside the submitted work. Cristina Ivanescu is an employee of IQVIA, which received funding from Astellas to conduct the statistical analyses for this work under consultancy contract. Krishnan Ramaswamy is an employee of Pfizer Inc. and reports stock ownership in Pfizer and stock ownership in Johnson & Johnson outside the submitted work. Fred Saad reports grants and personal fees, consulting/advisory role, and research funding from Astellas and Janssen during the conduct of the study; and grants and personal fees, consulting/advisory role, and research funding from Sanofi and Bayer outside the submitted work. Andrew J. Armstrong reports consultant/advisory role, research funding, and travel/accommodation/expenses from Astellas, and consultant/advisory role and

research funding from Pfizer and Medivation during the conduct of the study; grants, personal fees/consultant/advisory role, speakers bureau, institutional research funding, and travel/accommodation/expenses from Bayer; institutional grants/research funding from Novartis, Gilead Sciences, Roche/Genentech, Bristol-Myers-Squibb and Constellation; grants, personal fees/consulting/advisory role, and institutional research funding from Merck and AstraZeneca; honoraria, grants, personal fees/consultant/advisory role, institutional research funding, and travel/accommodation/expenses from Janssen; grants, personal fees/honoraria, consultant/advisory role, speakers bureau, institutional research funding, and travel/accommodation/expenses from Dendreon outside the submitted work.

Funding/support and role of the sponsor: The study was funded by Astellas Pharma Inc. and Pfizer Inc. The sponsors had a role in study design, data analysis and interpretation, and writing of the report. All authors had full access to all data and the corresponding author had final responsibility for the decision to submit for publication. The manuscript was written with editorial support from medical writers, funded by the sponsors. The authors developed the analysis plan and all stages of the manuscript in collaboration with Astellas and Pfizer.

Acknowledgments: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide. Medical writing support was provided by Tom Lavelle from Bioscript and editorial assistance by Beatrice Vetter-Ceriotti and Lauren Smith from Complete HealthVizion, all funded by the study sponsors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.03.019.

References

[1] US Food and Drug Administration. Highlights of prescribing information: XTANDI. www.accessdata.fda.gov/drugsatfda_docs/label/2019/203415s015lbl.pdf.
[2] Astellas Pharma US Inc. Xtandi summary of product characteristics. www.medicines.org.uk/emc/product/3203.
[3] Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 2015;16:509–21.
[4] Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. Ann Oncol 2015;26:179–85.
[5] Tombal B, Saad F, Penson D, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic castration-resistant prostate cancer (PROSPER): an international, randomised, phase 3 trial. Lancet Oncol 2019;20:556–69.
[6] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121–31.
[7] Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37:2974–88.
[8] Hall F, de Freitas HM, Kerr C, et al. Estimating utilities/disutilities for high-risk metastatic hormone-sensitive prostate cancer (mHSPC) and treatment-related adverse events. Qual Life Res 2019;28:1191–9.
[9] van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008;44:2418–24.
[10] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-prostate instrument. Urology 1997;50:920–8.
[11] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
[12] EuroQol. EQ-5D-5L user guide. https://euroqol.org/publications/user-guides/.
[13] Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. Eval Health Prof 2005;28:172–91.
[14] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.
[15] Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:287–94.
[16] Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
[17] Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health 2009;12:124–9.
[18] O'Kelly M, Ratitch B. Clinical trials with missing data: a guide for practitioners. Chichester, UK: John Wiley & Sons; 2014.
[19] Fairclough D. Design and analysis of quality of life studies in clinical trials. Boca Raton, FL: Chapman and Hall/CRC; 2010.
[20] Holzner B, Kemmler G, Cella D, et al. Normative data for functional assessment of cancer therapy—general scale and its use for the interpretation of quality of life scores in cancer survivors. Acta Oncol 2004;43:153–60.
[21] Washino S, Hirai M, Saito K, Kobayashi Y, Arai Y, Miyagawa T. Impact of androgen deprivation therapy on volume reduction and lower urinary tract symptoms in patients with prostate cancer. Lower urinary tract symptoms 2018;10:57–63.
[22] Prostate Cancer UK. Prostate Cancer UK hormone therapy. https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy.
[23] Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194–206.
[24] Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol 2019;20:1518–30.
[25] Morgans AK, Chen YH, Sweeney CJ, et al. Quality of life during treatment with chemohormonal therapy: analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer. J Clin Oncol 2018;36:1088–95.
[26] Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol 2013;14:1193–9.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Kidney Cancer

Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Metastatic Renal Cell Carcinoma

Bimal Bhindi[a,b,*], *Jeffrey Graham*[c], *J. Connor Wells*[d], *Ziad Bakouny*[e], *Frede Donskov*[f], *Anna Fraccon*[g], *Felice Pasini*[h], *Jae Lyun Lee*[i], *Naveen S. Basappa*[j], *Aaron Hansen*[k], *Christian K. Kollmannsberger*[l], *Ravindran Kanesvaran*[m], *Takeshi Yuasa*[n], *D. Scott Ernst*[o], *Sandy Srinivas*[p], *Brian I. Rini*[q], *Isaac Bowman*[r], *Sumanta K. Pal*[s], *Toni K. Choueiri*[e], *Daniel Y.C. Heng*[d]

[a] *University of Calgary, Calgary, AB, Canada;* [b] *Southern Alberta Institute of Urology, Calgary, AB, Canada;* [c] *CancerCare Manitoba, Winnipeg MB, Canada;* [d] *Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada;* [e] *Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [f] *Aarhus University Hospital, Aarhus, Denmark;* [g] *CDC Pererzoli, Peschiera del Garda, Italy;* [h] *Oncologia Medica Ospedale Santa Maria della Misericordia, Rovigo, Italy;* [i] *University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea;* [j] *University of Alberta, Edmonton, AB, Canada;* [k] *Princess Margaret Cancer Centre, Toronto, Canada;* [l] *British Columbia Cancer Agency, Vancouver, Canada;* [m] *National Cancer Centre Singapore, Singapore;* [n] *Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan;* [o] *Western University, London, ON, Canada;* [p] *Stanford Medical Center, Stanford, CA, USA;* [q] *Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA;* [r] *UT Southwestern Medical Center, Dallas, TX, USA;* [s] *City of Hope Comprehensive Cancer Center, Duarte, CA, USA*

Article info

Article history:
Accepted April 16, 2020

Associate Editor:
Todd Morgan

Stats Editor:
Melissa Assel

Keywords:
Cytoreduction surgical procedures
Nephrectomy
Neoplasm metastasis
Renal cell carcinoma
Targeted therapy
Tyrosine kinase inhibitor

Abstract

Background: The use of cytoreductive nephrectomy (CN) selectively for patients who show a favorable response to upfront systemic therapy may be an approach to select optimal candidates with metastatic renal cell carcinoma (mRCC) who are most likely to benefit.
Objective: We sought to characterize outcomes of deferred CN (dCN) after upfront sunitinib, outcomes relative to sunitinib alone, and outcomes of CN followed by sunitinib.
Design, setting, and participants: We used the prospectively maintained International mRCC Database Consortium (IMDC) database to identify patients with newly diagnosed mRCC (2006–2018).
Intervention: Sunitinib alone, upfront CN followed by sunitinib, sunitinib followed by dCN.
Outcome measurements and statistical analysis: Outcomes were overall survival (OS) and time to sunitinib treatment failure (TTF). Kaplan-Meier and multivariable Cox regression analyses were performed; dCN was analyzed as a time-varying covariate to account for immortal time bias.
Results and limitations: We evaluated 1541 patients, of whom 651 (42%) received sunitinib alone, 805 (52%) underwent CN followed by sunitinib, and 85 (5.5%) received sunitinib followed by dCN, at a median of 7.8 mo from diagnosis. Median OS periods for patients treated with sunitinib alone, CN followed by sunitinib, and sunitinib followed by dCN were 10, 19, and 46 mo, respectively, while the median TTF values were 4, 8, and

* Corresponding author. Southern Alberta Institute of Urology, Department of Surgery, Section of Urology, Cumming School of Medicine, University of Calgary, 6635, 7007 14thStreet SW, Calgary, AB T2V 1P9, Canada. Tel. +1 (403) 943-8964, Fax: +1 (403) 943-8919.
E-mail address: bimal.bhindi@gmail.com (B. Bhindi).

https://doi.org/10.1016/j.eururo.2020.04.038

13 mo, respectively. In multivariable regression analyses, sunitinib followed by dCN was significantly associated with improved OS (hazard ratio [HR] = 0.45, 95% confidence interval [CI] 0.33–0.60, $p < 0.001$) and TTF (HR = 0.62, 95% CI 0.46–0.85, $p = 0.003$) versus sunitinib alone. Among CN-treated patients, sunitinib followed by dCN was associated with improved OS (HR = 0.52, 95% CI 0.39–0.70, $p < 0.001$) and TTF (HR = 0.71, 95% CI 0.56–0.90, $p = 0.005$) compared with upfront CN followed by sunitinib. In various sensitivity analyses, dCN remained significantly associated with improved OS and TTF.
Conclusions: Patients who received dCN were carefully selected and achieved long OS. With these benchmark outcomes, optimal selection criteria need to be identified and confirmation of the role of dCN in a clinical trial is warranted.
Patient summary: We characterized benchmark survival outcomes for patients with metastatic kidney cancer treated with sunitinib alone, nephrectomy (kidney removal) followed by sunitinib, and sunitinib followed by nephrectomy. Patients who had their nephrectomy after an initial course of sunitinib had prolonged survival.

1. Introduction

During an era where cytokine therapies were the only systemic options for metastatic renal cell carcinoma (mRCC) and few patients survived beyond 2 yr [1], two randomized trials established a role for cytoreductive nephrectomy (CN) [2–4]. With the introduction of more effective systemic therapies [5], the role of CN has been revisited.

Retrospective data have supported an ongoing survival benefit associated with CN in mRCC in patients treated with targeted therapies [6–9]. However, the CARMENA trial found that sunitinib alone was noninferior to upfront CN followed by sunitinib in intermediate- and poor-risk mRCC patients [10].

It has been debated whether the trial's study population is representative of patients with mRCC selected for CN in real-world practice [11]. Furthermore, 17% of patients in the sunitinib-alone arm underwent a subsequent CN, which would bias results to finding no difference, given exceptionally long survival times in these patients [12].

Careful patient selection for upfront CN is essential, yet one of the greatest hindrances of upfront CN is that 15–30% of appropriately selected patients never receive systemic therapy, most often due to rapid disease progression or postoperative complications [6]. With increasingly effective systemic therapies, the harms of failing to receive systemic therapy may overshadow the benefits of CN.

Response to upfront systemic therapy has been proposed as a potential litmus test to better identify patients who may benefit from CN [13,14]. In this regard, CN can be used more selectively in the subset of patients with a favorable response to upfront systemic therapy. The SURTIME trial compared upfront versus deferred CN (dCN) strategies in patients with mRCC treated with sunitinib. Although the trial did not complete accrual and found no difference in its primary outcome of progression-free rate, there was a signal for an overall survival (OS) benefit in the deferred CN arm [15]. Others have also examined presurgical systemic therapy prior to planned CN in single-arm studies [13,14,16]. However, real-world outcome data are also needed to complement the data from patients specially selected for participation in these clinical trials.

As such, we sought to characterize outcomes of dCN after upfront sunitinib. Specifically, we sought to determine whether dCN is associated with improved survival in patients who have been treated with upfront sunitinib. We also sought to include patients who underwent CN followed by sunitinib as a comparison group. Our hypothesis was that patients undergoing sunitinib followed by dCN would have longer survival than patients receiving sunitinib alone and those receiving upfront CN followed by sunitinib.

2. Patients and methods

2.1. Study design, setting, and data collection

We conducted a retrospective analysis of an international, multicenter, prospectively maintained database of mRCC and have reported findings according to the STROBE guidelines [17]. Local ethics board approval was obtained at each center. Patients newly diagnosed with mRCC between 2006 and 2018 were identified from 33 participating centers in Canada, the USA, Belgium, Denmark, Germany, Greece, Italy, South Korea, Singapore, Japan, New Zealand, and Australia. Data collection using uniform database software and templates has been described previously [8]. Patient follow-up was according to local protocols.

2.2. Cohort inclusion and exclusion criteria

Only patients whose first systemic therapy was sunitinib were included. Exclusion criteria were first treatment (sunitinib or upfront CN) >12 mo after diagnosis, a period of surveillance of >6 mo after upfront CN (ie, sunitinib given >6 mo after upfront CN), unknown timing of dCN, and missing data on confounder variables (Supplementary Fig. 1).

2.3. Study exposure, outcomes, and covariates

Patients received upfront CN followed by sunitinib, sunitinib alone, or sunitinib followed by dCN, defined as any CN done after the receipt of upfront sunitinib. The primary outcome was OS, measured from the time of initiation of first treatment. The secondary outcome was time to treatment failure (TTF), defined as the time from the initiation of first treatment (upfront CN or upfront sunitinib) to the initiation of second-line systemic therapy or mortality.

Patients were grouped according to International mRCC Database Consortium (IMDC) risk classifications [18,19]. The best response to

sunitinib was categorized according to RECIST principles by the local investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

2.4. Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Baseline cohort characteristics were compared between groups using the Kruskal-Wallis and the chi-square tests for continuous and categorical variables, respectively. Survival curves were plotted using the Kaplan-Meier method in order to describe benchmark OS and TTF outcomes, and were compared using the log-rank test. Patients were censored if lost to follow-up or at the end of study follow-up if they did not experience the events of interest. The median follow-up time was estimated using the reverse Kaplan-Meier method [20].

Multivariable Cox proportional hazards models were then created, including a term for upfront CN (vs upfront sunitinib) and a term for dCN (as a time-varying covariate; vs sunitinib alone), and also including the following a priori selected potential confounders: upfront CN and dCN, age at diagnosis (continuous), sex, year of diagnosis (continuous), Karnofsky performance status (≥80 vs <80), IMDC risk group (intermediate vs poor risk; by definition, favorable-risk patients were not included), clear cell versus non–clear cell histology, sarcomatoid dedifferentiation, number of metastatic sites (continuous), and location of metastases (lung, brain, liver, bone, and lymph node). In order to account for immortal time bias, dCN was operationalized as a time-varying covariate [21]. In order to compare upfront CN followed by sunitinib versus upfront sunitinib followed by dCN strategies, separate models were made comparing these approaches in the subset of patients who underwent CN.

A subset analysis was performed on patients who received upfront sunitinib and had data available for the best response to sunitinib. First, we created additional multivariable models assessing the association between dCN and survival outcomes, and further adjusting for the type of response to sunitinib (PD, SD, or PR/CR) along with the previously mentioned covariates. Next, given that patients with PD may not be optimal candidates for dCN [13,14,16], we performed an additional subset analysis of patients with CR, PR, or SD to again evaluate the association between dCN and survival outcomes in this restricted subset using multivariable modeling.

Given evidence that the classical rule of 10 events per variable is not always required [22], the a priori plan was to include all clinically relevant potential confounders in the multivariable models provided that models did not appear overspecified. For further reassurance, we performed sensitivity analyses using backward selection (with threshold for model inclusion set at $p < 0.05$) and the change-of-estimate approach (whereby only covariates that changed the main effect estimate by >10% were included) [23–25] as variable reduction strategies, with the intent to reduce the number of variables in the model and to ensure that effect estimates remain stable.

Given that our priority was optimal control of confounders, the main analysis was performed on the complete case cohort. As a sensitivity analysis to ensure that bias was not being introduced by excluding patients with missing data on covariates, survival models with only dCN and upfront CN were run in the source cohort, including patients with missing covariates.

Finally, given that observation designs cannot entirely address unmeasured confounding, a sensitivity analysis without assumptions was performed. This sensitivity analysis evaluates the joint magnitude of the association between dCN and unmeasured confounders, and the association between unmeasured confounders and OS that would be necessary to explain away or invert the observed association between the initial treatment approach and OS [26–29].

Table 1 – Cohort characteristics.

Variable	Whole cohort ($n = 1541$)
Continuous variables, median (IQR)	
Age (yr)	61 (54–68)
Year of diagnosis	2011 (2008–2013)
No. of metastatic sites	2 (1–3)
Categorical variables, *n* (%)	
Female sex	403 (26)
Karnofsky performance <80	427 (28)
Poor IMDC risk (vs. intermediate)	618 (40)
Clear cell histology	1311 (85)
Sarcomatoid dedifferentiation	232 (15)
Brain metastasis	130 (8)
Lung metastasis	1141 (74)
Liver metastasis	333 (22)
Bone metastasis	593 (38)
Nodal metastasis	785 (51)
Other metastatic site	461 (30)
Number of metastatic sites	
1	435 (28)
2	546 (35)
3	371 (24)
4	147 (10)
5+	42 (3)

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IQR = interquartile range.

All hypothesis tests were two sided, and $p < 0.05$ was considered statistically significant.

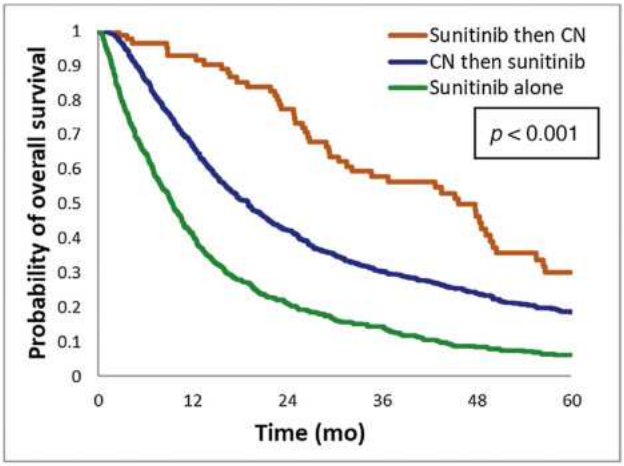
3. Results

The final cohort included 1541 patients with newly diagnosed mRCC, of whom 805 received upfront CN followed by sunitinib, 651 received sunitinib alone, and 85 received sunitinib followed by dCN at a median of 7.8 mo (interquartile range [IQR] 4.8–12.6) from the date of initiation of sunitinib (Supplementary Fig. 1). Cohort characteristics are described in Table 1. Patients who received sunitinib alone were slightly older at diagnosis and were more likely to have diminished Karnofsky performance status, IMDC poor-risk disease, and a greater number of metastatic sites.

There were 1202 deaths, and 1415 patients experienced sunitinib treatment failure. Median follow-up among survivors from first treatment initiation was 25 mo (IQR 10–49).

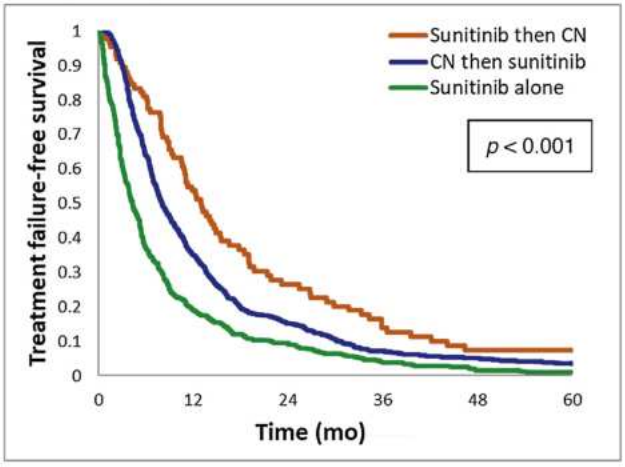
3.1. Overall survival

The OS for each group is shown in Fig. 1A. The median OS times for patients treated with sunitinib alone, CN followed by sunitinib, and sunitinib followed by CN were 10 (IQR 4–20), 19 (IQR 9–46), and 46 (IQR 25–67) mo, respectively. Upon multivariable adjustment and accounting for immortal time bias, upfront CN followed by sunitinib versus sunitinib alone remained significantly associated with improved OS (hazard ratio [HR] = 0.60, 95% confidence interval [CI] 0.53–0.68, $p < 0.001$), as did sunitinib followed by dCN versus sunitinib alone (HR = 0.45, 95% CI 0.33–0.60,



Time (mo)	0	12	24	36	48	60
Sunitinib then CN	85	76	58	38	26	14
CN then sunitinib	805	497	272	157	110	69
Sunitinib alone	651	246	121	70	35	21

A



Time (mo)	0	12	24	36	48	60
Sunitinib then CN	85	45	21	11	6	5
CN then sunitinib	805	263	99	41	28	16
Sunitinib alone	651	112	52	18	7	3

B

Fig. 1 – Overall survival and time to treatment failure in the main cohort: (A) overall survival and (B) time to treatment failure. CN = cytoreductive nephrectomy.

$p < 0.001$; Table 2). Among CN-treated patients, sunitinib followed by dCN was associated with improved OS compared with upfront CN followed by sunitinib (HR = 0.52; 95% CI 0.39–0.70, $p < 0.001$; Table 2).

3.2. Time to treatment failure

The TTF for each group is shown in Fig. 1B. The median TTF values for patients treated with sunitinib alone, CN followed by sunitinib, and sunitinib followed by CN were 4 (IQR 2–9), 8 (IQR 5–16), and 13 (IQR 8–27) mo, respectively. Upon multivariable adjustment and accounting for immortal time bias, upfront CN followed by sunitinib versus sunitinib alone remained significantly associated with improved TTF (HR = 0.68, 95% CI 0.61–0.76, $p < 0.001$), as did sunitinib followed by dCN versus sunitinib alone (HR = 0.62, 95% CI 0.46–0.85, $p = 0.003$; Table 2). Among CN-treated patients, sunitinib followed by dCN was associated with improved TTF compared with upfront CN followed by sunitinib (HR = 0.71, 95% CI 0.56–0.90, $p = 0.005$; Table 2).

3.3. Subset analysis of patients treated with sunitinib alone and available response data

A total of 619 patients receiving upfront sunitinib had data available on the best response to sunitinib. Patients who received subsequent dCN were more likely to have had a PR or a CR (Supplementary Table 1). To account for this, a multivariable analysis further adjusting for the type of response was performed on this subset, and it was found that dCN remained significantly associated with improved OS (HR = 0.39, 95% CI 0.28–0.54, $p < 0.001$) and TTF (HR = 0.48, 95% CI 0.34–0.68, $p < 0.001$; Table 3).

Given that patients with PD may not be ideal candidates for dCN, and that those who underwent and who did not undergo dCN with PD may be unmeasurably different, a sensitivity analysis excluding patients with PD was performed. Of note, the interaction term between dCN and response type was significant for OS and TTF (both $p < 0.001$). Among patients receiving upfront sunitinib, median OS periods without and with dCN were 16 (IQR 9–32) and 46 (IQR 25–67) mo, respectively ($p < 0.001$; Fig. 2A), while median TTF values without and with dCN were 8 (IQR 5–16) and 14 (IQR 9–27) mo, respectively ($p < 0.001$; Fig. 2B). Upon multivariable analysis, which additionally adjusted for these types of responses, dCN remained significantly associated with OS (HR = 0.58, 95% CI 0.40–0.84, $p = 0.004$) and TTF (HR = 0.67, 95% CI 0.48–0.92, $p = 0.01$; Table 3).

There was no evidence that multivariable models were overspecified. Sensitivity analyses using backward selection and the change-of-estimate approaches produced more parsimonious models and yielded stable effect estimates compared with the main analysis (Supplementary material). Sensitivity analyses that did not exclude patients with missing variables yielded similar results to our main analysis (Supplementary material). Another sensitivity analysis was performed requiring tighter timelines from initial diagnosis to first treatment (CN or sunitinib; 3 mo

Table 2 – Multivariable models for whole cohort analysis.

	HR (95% CI)	*p* value
Overall survival		
Model 1		
Upfront CN then sunitinib (vs upfront sunitinib)[a]	0.60 (0.53–0.68)	<0.001
Sunitinib then dCN (vs sunitinib alone)[a]	0.45 (0.33–0.60)	<0.001
Model 2		
Sunitinib then dCN (vs upfront CN then sunitinib)[b]	0.52 (0.39–0.70)	<0.001
Treatment failure–free survival		
Model 3		
Upfront CN then sunitinib (vs upfront sunitinib)[a]	0.68 (0.61–0.76)	<0.001
Sunitinib then CN (vs sunitinib alone)[a]	0.62 (0.46–0.85)	0.003
Model 4		
Sunitinib then dCN (vs upfront CN then sunitinib)[b]	0.71 (0.56–0.90)	0.005

CI = confidence interval; CN = cytoreductive nephrectomy; dCN = deferred cytoreductive nephrectomy; HR = hazard ratio; mRCC = metastatic renal cell carcinoma.
Models adjusted for upfront CN and dCN, age at diagnosis (continuous), sex, year of diagnosis (continuous), Karnofsky performance status (≥80 vs <80), International mRCC Database Consortium (IMDC) risk group (intermediate vs poor risk; by definition, favorable-risk patients were not included), clear cell versus non–clear cell histology, sarcomatoid dedifferentiation, number of metastatic sites (continuous), and location of metastases (lung, brain, liver, bone, and/or lymph node).
[a] The first set of models included all patients in the model. This model included a term for "upfront CN then sunitinib" (vs upfront sunitinib) and a term for "sunitinib then dCN" (vs sunitinib alone) in the same model, the latter of which was a time-varying covariate.
[b] The second set of models evaluated the subset of patients who had CN, directly comparing "sunitinib followed by dCN" versus "upfront CN followed by sunitinib" strategies (n = 890).

instead of 12 mo) and for sunitinib to be after upfront CN (3 mo instead of 6 mo). This sensitivity analysis yielded similar results to our main analysis (data not shown). Another sensitivity analysis was performed including the receipt of sunitinib as a time-varying covariate, which also yielded similar results (data not shown). Finally, our sensitivity analysis without assumptions found that in order to explain away the association between dCN and OS that was no longer significant, a strong association between the receipt of dCN and unmeasured confounders, and jointly a strong association between unmeasured confounders and OS, would be required (Supplementary Table 2).

4. Discussion

The present analysis provides real-world benchmark OS and TTF outcomes for patients with newly diagnosed mRCC treated with sunitinib alone, CN followed by sunitinib, and sunitinib followed by dCN. Notably, patients with mRCC treated with sunitinib followed by dCN achieved prolonged OS and TTF when appropriately selected. Furthermore, upon adjusting for confounders and type of response to sunitinib, dCN remained significantly associated with improved OS and TTF. This analysis of patients treated during the targeted therapy era supports the use of dCN among patients receiving upfront tyrosine kinase inhibitors in select cases.

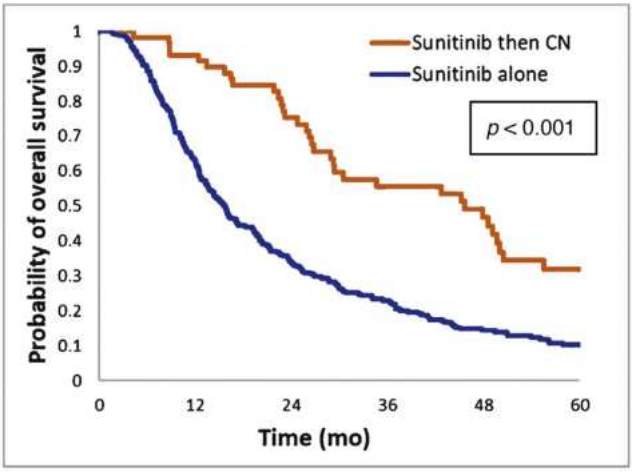
Our data closely mirror the findings of a secondary analysis of the CARMENA trial presented at the American Society of Clinical Oncology (ASCO) 2019 annual meeting, where it was found that, in the sunitinib-alone arm, secondary nephrectomy was associated with improved OS compared with no nephrectomy (median OS: 48.5 vs 15.7 mo; HR = 0.34, 95% CI 0.22–0.54) [12]. Meanwhile, OS of patients who underwent dCN in studies of the National Cancer Database were at least similar to, if not longer than, the OS of those who underwent upfront CN, presumably due to being selected as having more favorable biology based on passing a systemic therapy litmus test [27,30].

One of the major reservations regarding the upfront treatment of mRCC with CN is the risk of not receiving

Table 3 – Subgroup analyses of patients receiving upfront sunitinib, further adjusting for the type of response to sunitinib.

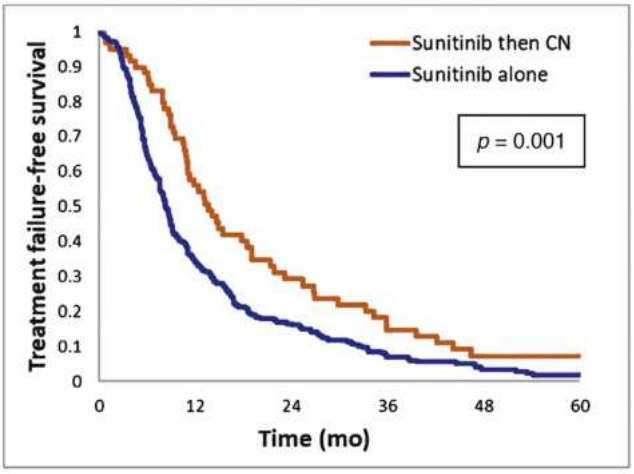
	HR (95% CI)	*p* value
Effect of deferred CN on overall survival		
All patients receiving upfront sunitinib	0.39 (0.28–0.54)	<0.001
Subset with CR/PR/SD	0.58 (0.40–0.84)	0.004
Effect of deferred CN on treatment failure–free survival		
All patients receiving upfront sunitinib	0.48 (0.34–0.68)	<0.001
Subset with CR/PR/SD	0.67 (0.48–0.92)	0.01

CI = confidence interval; CN = cytoreductive nephrectomy; CR = complete response; dCN = deferred cytoreductive nephrectomy; HR = hazard ratio; mRCC = metastatic renal cell carcinoma; PD = progressive disease; PR = partial response; SD = stable disease.
Models adjusted for upfront CN and dCN, age at diagnosis (continuous), sex, year of diagnosis (continuous), Karnofsky performance status (≥80 vs <80), International mRCC Database Consortium (IMDC) risk group (intermediate vs poor risk; by definition, favorable-risk patients were not included), clear cell versus non–clear cell histology, sarcomatoid dedifferentiation, number of metastatic sites (continuous), location of metastases (lung, brain, liver, bone, and/or lymph node), and type of response to upfront sunitinib (CR/PR, SD, PD).



Time (mo)	0	12	24	36	48	60
Sunitinib then CN	59	55	40	27	19	11
Sunitinib alone	325	194	100	59	31	20

A



Time (mo)	0	12	24	36	48	60
Sunitinib then CN	59	33	16	8	4	4
Sunitinib alone	325	104	47	17	7	3

B

Fig. 2 – Subset analysis of patients treated with upfront sunitinib with stable disease, partial response, or complete response: (A) overall survival and (B) time to treatment failure. CN = cytoreductive nephrectomy.

subsequent systemic therapy in 15–30% of patients, most often due to rapid disease progression or postoperative complications [6]. In the CARMENA trial, 18% of patients randomized to upfront CN did not receive postoperative sunitinib [10]. Not receiving sunitinib may have overshadowed any potential survival benefit provided by CN. In contrast, not receiving cytokine therapies in the trials from the cytokine era [2–4] may not be as impactful. This may, in part, explain why CN resulted in improved survival in trials from the cytokine era [2–4] but not in CARMENA [10].

An initial course of systemic therapy may be a way to identify patients with aggressive biology destined to do poorly. Indeed, phase II trials have supported the use of upfront systemic therapy as a litmus test to aid in the selection of patients for CN [13,14]. For example, Powles et al [13] reported a phase II trial of 66 patients who received presurgical sunitinib prior to planned CN, of whom 27% had disease progression prior to or at the time of planned surgery. Patients with Memorial Sloan Kettering Cancer Center intermediate- and poor-risk disease who had disease progression on presurgical sunitinib had median OS times of 3 and 1 mo, respectively; progression prior to planned surgery was strongly associated with worse OS (HR = 5.34, 95% CI 2.74–11.62). These data were then validated by Powles et al [14] in a phase II trial of 104 patients receiving presurgical pazopanib prior to planned CN. In this study, 16% had PD and did not proceed to surgery, while 84% of patients achieved "clinical benefit" with pazopanib, defined as no clinical or radiographic progression while on presurgical pazopanib. Similarly to sunitinib, patients who had PD on pazopanib had shorter OS compared with those who achieve clinical benefit (median OS 3.9 vs 24.0 mo, HR = 3.92, 95% CI 1.78–8.63). As such, upfront systemic therapy identified patients with PD who would be unlikely to benefit from CN and allowed the use of dCN in a clearer subset of patients who are more likely to benefit.

Despite existing literature, optimal patient selection remains to be defined. The phase II trials by Powles and colleagues [13,14] had 61–71% of patients undergoing dCN. The reason for not undergoing dCN was primarily PD on sunitinib or patient choice. Meanwhile, 17% of patients in the sunitinib-alone arm of CARMENA underwent dCN, primarily those with strong PRs or CRs [10]. While the proportion of responders is expected to increase in the immuno-oncology (IO) era, the optimal proportion of patients to submit to CN remains to be defined.

Strengths of our study include the use of a large, international, multicenter, prospectively maintained registry of patient with mRCC with long follow-up, and its consistency with existing literature. Furthermore, data on IMDC risk factors, performance status, metastatic burden, and response to systemic therapy allowed for more granular risk adjustment between groups. There are also limitations worth mentioning. First, as with all observational studies, it is not possible to account for unmeasured differences between groups that may have influenced treatment selection. For example, individual comorbidity data were not available, although performance status was captured. Our sensitivity analysis without assumptions suggests that this effect would have to be quite strong to explain away the observed associations. Second, given that this database depends on patients receiving systemic therapy, it is unknown how many patients underwent upfront CN and did not receive subsequent sunitinib, which may have

impacted survival times in the upfront CN group. Third, we focused on patients treated with sunitinib to allow for a more homogenous cohort. Given that phase II data on presurgical sunitinib and pazopanib are similar [13,14], it is likely that our data also apply to patients treated with pazopanib. It remains to be determined how dCN will play a role in patients treated with IO-based combination therapy; analyses evaluating upfront CN and dCN in IO-treated patients in the IMDC are underway. Additionally, two prospective randomized studies will further clarify the impact of dCN in IO-treated patients: NORDIC-SUN (ClinicalTrials.gov: NCT03977571) and SWOG-1931. Notably, the efficacy of IO-based therapies have been established in trial populations where >80% of patients have had prior nephrectomy [31–33]. Further understanding of the role of CN in these patients will improve as data on these patients mature. Fourth, we did not have data on metastasis-directed therapy, but it may have played a role in the prolonged OS observed in the dCN group. Metastasis-directed therapy should be considered an important component of cytoreductive strategies, particularly in light of data suggesting prolonged survival when complete metastasectomy can be achieved [34]. Finally, we did not have data on the indication for dCN. It is likely that a minority were done for controlling hemorrhage or palliation. Furthermore, given the poor prognosis in such patients, it is likely, if anything, that their inclusion in the dCN group would bias results toward the null.

5. Conclusions

Our data support the use of dCN among selected patients with mRCC after upfront systemic therapy. Further validation of the role of dCN is urgently warranted, ideally in the setting of a clinical trial using IO-based combination therapy. However, in the meantime, dCN should remain a therapeutic consideration for selected patients, given that, even in the most conservative scenario, dCN was an important component of therapy provided in the "sunitinib-only" control arm of the CARMENA trial.

***Author contributions*:** Bimal Bhindi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bhindi, Heng.
Acquisition of data: Heng, Graham, Wells, Donskov, Fraccon, Pasini, Lee, Basappa, Hansen, Kollmannsberger, Kanesvaran, Yuasa, Ernst, Srinivas, Rini, Bowman, Pal, Choueiri.
Analysis and interpretation of data: Bhindi, Graham, Wells, Bakouny, Donskov, Fraccon, Pasini, Lee, Basappa, Hansen, Kollmannsberger, Kanesvaran, Yuasa, Ernst, Srinivas, Rini, Bowman, Pal, Choueiri, Heng.
Drafting of the manuscript: Bhindi.
Critical revision of the manuscript for important intellectual content: Bhindi, Graham, Wells, Bakouny, Donskov, Fraccon, Pasini, Lee, Basappa, Hansen, Kollmannsberger, Kanesvaran, Yuasa, Ernst, Srinivas, Rini, Bowman, Pal, Choueiri, Heng.
Statistical analysis: Bhindi, Wells.
Obtaining funding: None.
Administrative, technical, or material support: Wells, Graham, Heng.
Supervision: None.
Other: None.

Financial disclosures: Bimal Bhindi certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Bimal Bhindi: honoraria—Merck; advisory board—Janssen and Bayer. Jeffrey Graham: honoraria/consulting—Janssen and Pfizer. Connor Wells: travel, accommodations, and expenses—Pfizer. Ziad Bakouny: no disclosures. Frede Donskov: research funding—Ipsen (Inst), Novartis (Inst), and Pfizer (Inst). Anna Fraccon and Felice Pasini: no relationships to disclose. Jae-Lyun Lee: honoraria—Amgen Korea, Astellas Pharma, and Bristol-Myers Squibb; consulting or advisory role—BMS Korea, Eisai, Pfizer Korea, and Sanofi Aventis Korea; research funding—AstraZeneca/MedImmune (Inst), Bristol-Myers Squibb (Inst), Janssen (Inst), MSD (Inst), Novartis (Inst), Pfizer (Inst), and Roche/Genentech (Inst). Naveen S. Basappa: honoraria—Astellas Pharma, Eisai, Ipsen, Janssen, Merck, and Pfizer; consulting or advisory role—Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Ipsen, Janssen, Merck, Pfizer, Roche Canada; travel, accommodations, and expenses—Janssen. Aaron Richard Hansen: honoraria—AstraZeneca/MedImmune, Bristol-Myers Squibb, GlaxoSmithKline/Novartis, Merck, and Pfizer; consulting or advisory role—Boehringer Ingelheim, Boston Biomedical, Bristol-Myers Squibb, Genentech/Roche, GlaxoSmithKline, Merck, and Novartis; research funding—Boehringer Ingelheim, Bristol-Myers Squibb (Inst), GlaxoSmithKline (Inst), Karyopharm Therapeutics (Inst), Merck (Inst), and Novartis (Inst). Christian K. Kollmannsberger: honoraria—Bristol-Myers Squibb, Novartis, and Pfizer; consulting or advisory role—Astellas Pharma, Bristol-Myers Squibb, Eisai, Ipsen, Novartis, and Pfizer; travel, accommodations, and expenses—Novartis and Pfizer. Ravindran Kanesvaran: honoraria—Astellas Pharma, Bristol-Myers Squibb, Janssen, MSD Oncology, and Novartis; consulting or advisory role—Astellas Pharma, Mundipharma, Novartis, and Pfizer; research funding—Janssen (Inst) and Sanofi (Inst); travel, accommodations, and expenses—Astellas Pharma, Bristol-Myers Squibb, and MSD Oncology. Takeshi Yuasa: no relationships to disclose. D. Scott Ernst: consulting or advisory role—AstraZeneca/MedImmune, Bristol-Myers Squibb, EMD Serono, Merck, Novartis Canada Pharmaceuticals Inc, and Sanofi Canada. Sandy Srinivas: consulting or advisory role—Genentech/Roche; speakers' bureau—Genentech; research funding—Bristol-Myers Squibb (Inst), Exelixis (Inst), Genentech (Inst), and Merck (Inst). Brian I. Rini: consulting or advisory role—AVEO, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Roche/Genentech, and Synthorx; research funding—AstraZeneca/MedImmune (Inst), AVEO (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Peloton Therapeutics (Inst), Pfizer (Inst), Roche/Genentech (Inst); travel, accommodations, and expenses—Bristol-Myers Squibb, Merck, and Pfizer. I. Alex Bowman: no relationships to disclose. Sumanta K. Pal: honoraria—Astellas Pharma, Medivation, and Novartis; consulting or advisory role—Astellas Pharma, Aveo, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Ipsen, Myriad Pharmaceuticals, Novartis, and Pfizer; research funding—Medivation. Toni K. Choueiri: employment—Dana Farber Cancer Hospital; leadership—Dana Farber Cancer Hospital, Kidney Cancer Association, and NCCN; honoraria—Alexion Pharmaceuticals, Alligent, Analysis Group, ASCO, AstraZeneca, Bayer, Bristol-Myers Squibb, Cerulean Pharma, Clinical Care Options, Corvus Pharmaceuticals, Eisai, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, GlaxoSmithKline, Harborside Press, HERON, Ipsen, Kidney Cancer Journal, Lancet Oncology, Lilly, Lpath, Merck, Michael J. Hennessy Associates, Navinata Healthcare, NCCN, NEJM, Novartis, Peloton Therapeutics, Pfizer, PlatformQ Health, Prometheus, Sanofi/Aventis, and UpToDate; consulting or advisory role—

Alexion Pharmaceuticals, Alligent, Analysis Group, ASCO, AstraZeneca, Bayer, Bristol-Myers Squibb, Cerulean Pharma, Clinical Care Options, Corvus Pharmaceuticals, Eisai, EMD Serono, Exelixis, Foundation Medicine, GlaxoSmithKline, Harborside Press, HERON, Ipsen, Kidney Cancer Journal, Lancet Oncology, Lilly, Lpath, Merck, Michael J. Hennessy Associates, Navinata Healthcare, NCCN, NEJM, Novartis, PlatformQ, Peloton Therapeutics, Pfizer, Prometheus Laboratories, Roche/Genentech, Sanofi/Aventis, and UpToDate; research funding—Agensys (Inst), Analysis Group (Inst), AstraZeneca (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Calithera Biosciences (Inst), Celldex (Inst), Cerulean Pharma (Inst), Corvus Pharmaceuticals (Inst), Eisai (Inst), Exelixis (Inst), Foundation Medicine (Inst), GlaxoSmithKline (Inst), Ipsen (Inst), Merck (Inst), Novartis (Inst), Peloton Therapeutics (Inst), Pfizer (Inst), Prometheus (Inst), Roche (Inst), Roche/Genentech (Inst), Seattle Genetics/Astellas (Inst), Takeda (Inst), and TRACON Pharma (Inst); other relationship—medical writing and editorial assistance support may have been funded by Communications companies funded by pharmaceutical companies such as ClinicalThinking, Health Interactions, Envision Pharma Group, Fishawack Group of Companies, and Parexel. Daniel Yick Chin Heng: consulting or advisory role—Astellas Pharma, Bristol-Myers Squibb, Eisai, Ipsen, Janssen, Merck, Novartis, and Pfizer; research funding—Bristol-Myers Squibb (Inst), Exelixis (Inst), Ipsen (Inst), Novartis (Inst), and Pfizer (Inst).

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.04.038.

References

[1] Marcus SG, Choyke PL, Reiter R, et al. Regression of metastatic renal cell carcinoma after cytoreductive nephrectomy. J Urol 1993;150:463–6.
[2] Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H. Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071–6.
[3] Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–9.
[4] Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–70.
[5] Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354–66.
[6] Bhindi B, Abel EJ, Albiges L, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. Eur Urol 2019;75:111–28.
[7] Graham J, Bhindi B, Heng DYC. The evolving role of cytoreductive nephrectomy in metastatic renal cell carcinoma. Curr Opin Urol 2019;29:507–12.
[8] Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 2014;66:704–10.
[9] Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol 2011;185:60–6.
[10] Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379:417–27.
[11] Arora S, Sood A, Dalela D, et al. Cytoreductive nephrectomy: assessing the generalizability of the CARMENA trial to real-world National Cancer Data Base cases. Eur Urol 2019;75:352–3.
[12] Mejean A, Thezenas S, Chevreau C, et al. Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): update on CARMENA trial with focus on intermediate IMDC-risk populationAmerican Society of Clinical Oncology Annual Meeting; Chicago, IL, USA; 2019.
[13] Powles T, Blank C, Chowdhury S, et al. The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer. Eur Urol 2011;60:448–54.
[14] Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. JAMA Oncol 2016;2:1303–9.
[15] Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. JAMA Oncol 2019;5:164–70.
[16] Jonasch E, Wood CG, Matin SF, et al. Phase II presurgical feasibility study of bevacizumab in untreated patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:4076–81.
[17] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
[18] Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141–8.
[19] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794–9.
[20] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[21] Austin PC, Mamdani MM, van Walraven C, Tu JV. Quantifying the impact of survivor treatment bias in observational studies. J Eval Clin Pract 2006;12:601–12.
[22] Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–8.
[23] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[24] Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923–36.
[25] Nayan M, Bhindi B, Yu JL, et al. The effect of metformin on cancer-specific survival outcomes in diabetic patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Urol Oncol 2015;33, 386.e7–13.
[26] Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology 2016;27:368–77.
[27] Bhindi B, Habermann EB, Mason RJ, et al. Comparative survival following initial cytoreductive nephrectomy versus initial targeted therapy for metastatic renal cell carcinoma. J Urol 2018;200:528–34.
[28] Bhindi B, Rangel LJ, Mason RJ, et al. Impact of radical prostatectomy on long-term oncologic outcomes in a matched cohort of men with pathological node positive prostate cancer managed by castration. J Urol 2017;198:86–91.

[29] Seisen T, Sun M, Leow JJ, et al. Efficacy of high-intensity local treatment for metastatic urothelial carcinoma of the bladder: a propensity score-weighted analysis from the National Cancer Data Base. J Clin Oncol 2016;34:3529–36.
[30] Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a National Cancer Data Base Study. J Clin Oncol 2016;34:3267–75.
[31] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.
[32] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.
[33] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27.
[34] Zaid HB, Parker WP, Safdar NS, et al. Outcomes following complete surgical metastasectomy for patients with metastatic renal cell carcinoma: a systematic review and meta-analysis. J Urol 2017;197:44–9.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Case Series of the Month

Urinary Frequency as a Possibly Overlooked Symptom in COVID-19 Patients: Does SARS-CoV-2 Cause Viral Cystitis?

Jan-Niclas Mumm[a,*], *Andreas Osterman*[b,c], *Michael Ruzicka*[d], *Clemens Stihl*[e], *Theresa Vilsmaier*[f], *Dieter Munker*[g], *Elham Khatamzas*[d], *Clemens Giessen-Jung*[d], *Christian Stief*[a], *Michael Staehler*[a], *Severin Rodler*[a]

[a] *Klinik und Poliklinik für Urologie, Klinikum der Universität München, Munich, Germany;* [b] *National Reference Center for Retroviruses, Max von Pettenkofer Institute and Gene Center, Faculty of Medicine, LMU München, Munich, Germany;* [c] *German Center for Infection Research, Munich Partner Site, Munich, Germany;* [d] *Medizinische Klinik III, Klinikum der Universität München, Munich, Germany;* [e] *Klink für Hals-Nasen-Ohren-Heilkunde, Klinikum der Universität München, Munich, Germany;* [f] *Klink für Frauenheilkunde, Klinikum der Universität München, Munich, Germany;* [g] *Medizinische Klinik V, Klinikum der Universität München, Munich, Germany*

Article info

Article history:
Accepted May 12, 2020

Associate Editor:
James Catto

Keywords:
COVID-19
Urinary frequency
Urinary infection
Triage
Viral cystitis

Abstract

The current coronavirus disease 2019 (COVID-19) pandemic is a challenge for physicians in triaging patients in emergency rooms. We found a potentially dangerous overlap of classical urinary symptoms and the as yet not fully described symptoms of COVID-19. After a patient was primarily triaged as a urosepsis case and then subsequently diagnosed with COVID-19, we focused on an increase in urinary frequency as a symptom of COVID-19 and identified this in seven males out of 57 patients currently being treated in our COVID-19 wards. In the absence of any other causes, urinary frequency may be secondary to viral cystitis due to underlying COVID-19 disease. We propose consideration of urinary frequency as an anamnestic tool in patients with infective symptoms to increase awareness among urologists during the current COVID-19 pandemic to prevent fatal implications of misinterpreting urological symptoms.

* Corresponding author. Klinik für Urologie, Klinikum der Universität München, Marchioninistrae 15, 81377 Munich, Germany. Tel. +49 89 440075970, Fax: +49 89 440076532.
E-mail address: janniclas.mumm@med.uni-muenchen.de (J.-N. Mumm).

1. Case series

1.1. Background

After its initial discovery in Wuhan, China the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread throughout the world and the consecutive coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization shortly afterwards [1]. As the pandemic is still in an early phase and many symptoms have not yet been fully described [2], careful clinical observation is of paramount importance. Rocco et al [3] pointed out the importance of early recognition of symptoms by urologists for proper triage of patients and to prevent missing possible SARS-CoV-2 infection because of an overlap of COVID-19 and classical urological symptoms. We believe that in addition to fever, an increase in urinary frequency should be considered as an important

https://doi.org/10.1016/j.eururo.2020.05.013
0302-2838/

overlapping symptom with urosepsis in the differential diagnosis of COVID-19 both in ambulatory care and in emergency rooms.

1.2. Cases

A case with suspected urinary sepsis was admitted to the emergency department of a university hospital. The patient reported fever, shivering, flank pain, urgency, and increased urinary frequency as initial symptoms. Initial urine analysis via urine sediment and urine culture demonstrated no signs of infection. The patient was discharged home with oral antibiotics. As part of the routine work-up in German hospitals, a nasopharyngeal swab that had been taken on the same day revealed a positive result for SARS-CoV-2 by polymerase chain reaction (PCR) the following day. Subsequently, the patient was admitted to one of our specialized COVID-19 wards with aggravating symptoms including fever, fatigue, and breath-dependent chest pain.

Urinary frequency is a common symptom in urinary infection. In order to investigate if this was present in other patients with COVID-19, we retrospectively and prospectively looked at patient histories for the presence of urinary frequency on admission to our specialized COVID-19 wards. In the time period from March 16 to April 13, 2020, seven males out of 57 patients reported an increase in urinary frequency along with dry cough (n = 5), fever (n = 3), and shortness of breath (n = 3) as leading symptoms (Tables 1 and 2). All patients tested positive for SARS-CoV-2 in nasopharyngeal swabs and developed pulmonary symptoms detectable on imaging (Fig. 1). Micturition protocol revealed an average of 13.7 micturitions per day on the day of admission and 11.6 on day 5. In all patients, urinary infection, acute renal injury, and prostatitis were excluded by urine analysis and normal serum creatinine and prostate-specific antigen (PSA), respectively. Prostate volumes were evaluated via ultrasound, which revealed mildly enlarged prostates in all patients; there were no signs of residual urine or significant bladder wall thickening. SARS-CoV-2 RNA was not detected by PCR in any urinary specimens taken from all the patients during the first week after admission. Two patients had detectable SARS-CoV-2 RNA in serum during this period (Ct value 40; Tables 3 and 4). None of the patients required admission to the intensive care unit. The average length of stay was 15 d.

Table 1 – Patient characteristics.

Parameter	Result
Median age, yr (range)	62 (59–78)
Median MuLBSTA score (range) [a]	9 (6–15)
Male, *n* (%)	7 (100)
Chronic underlying condition, *n* (%)	
Hypertension	5 (71.4)
Cardiac disease	2 (28.6)
Obesity	2 (28.6)
Diabetes	2 (28.6)
Cancer	2 (28.6)
Renal disease	1 (14.3)
Benign prostatic hyperplasia	1 (14.3)

[a] The MuLBSTA score is used to predict 90-d mortality in viral pneumonia [10].

Table 2 – Symptoms on admission.

Symptom	Patients, *n* (%)
Increased urinary frequency	7 (100)
Dry cough	5 (71.4)
Fever	3 (42.9)
Shortness of breath	3 (42.9)
Diarrhea	1 (14.3)
Shivering	1 (14.3)

2. Discussion

The reason for higher urinary frequency is unclear so far, as the patients had no signs of acute kidney injury, bacterial infection, or prostatitis. We suspect that viral cystitis due to SARS-CoV-2 causes the urinary frequency symptom. It is unclear whether replication of SARS-CoV-2 RNA in urothelial cells or secondary effects due to local or systemic inflammation, such as endotheliitis [4], are a hallmark in COVID-19 patients leading to symptoms such as irritative symptoms of the lower urinary tract and high urinary frequency. Interestingly, three patients presented with microhematuria, which possibly further supports the hypothesis of SARS-CoV-2–induced viral cystitis on infection of urothelial cells. Conversely, we did not detect viral RNA in the urine of these patients, so it seems that urine is unlikely to be a potential source of infection, at least in our cohort.

2.1. Potential mode of action

Recent studies revealed the cell-surface protein angiotensin-converting enzyme 2 (ACE2) as the main receptor for the SARS-CoV-2 spike protein [5]. Investigations of the distribution across many different tissues revealed that ACE2 expression was highest in lung, intestines, and kidney, but it was also high in 2.4% of urothelial cells, potentially increasing their susceptibility to infection with SARS-CoV-2 and possible subsequent viral cystitis [6]. As viral RNA has been detected in urine of COVID-19 patients [7], it can be hypothesized that infection of tissues of the urinary tract might cause an increase in urinary frequency. Detection of SARS-CoV-2 RNA in serum of two hospitalized patients, similar to detection of elevated IL-6 [8], is suggestive of the assumption that urinary frequency occurs as a complication in these patients in the course of a more severe stage of infection. Despite the presence of ACE2 in the urogenital tract, negative urinary PCR results do not support the assumption of strong or even relevant continuous replication in (luminal) tissues of the efferent urinary tract. Since it is unclear whether the receptor is expressed in luminal or basal urothelial cells, the route by which SARS-CoV-2 might cause viral cystitis could be via either viremia from the basal side or urine from the luminal side of urothelial tissue. The

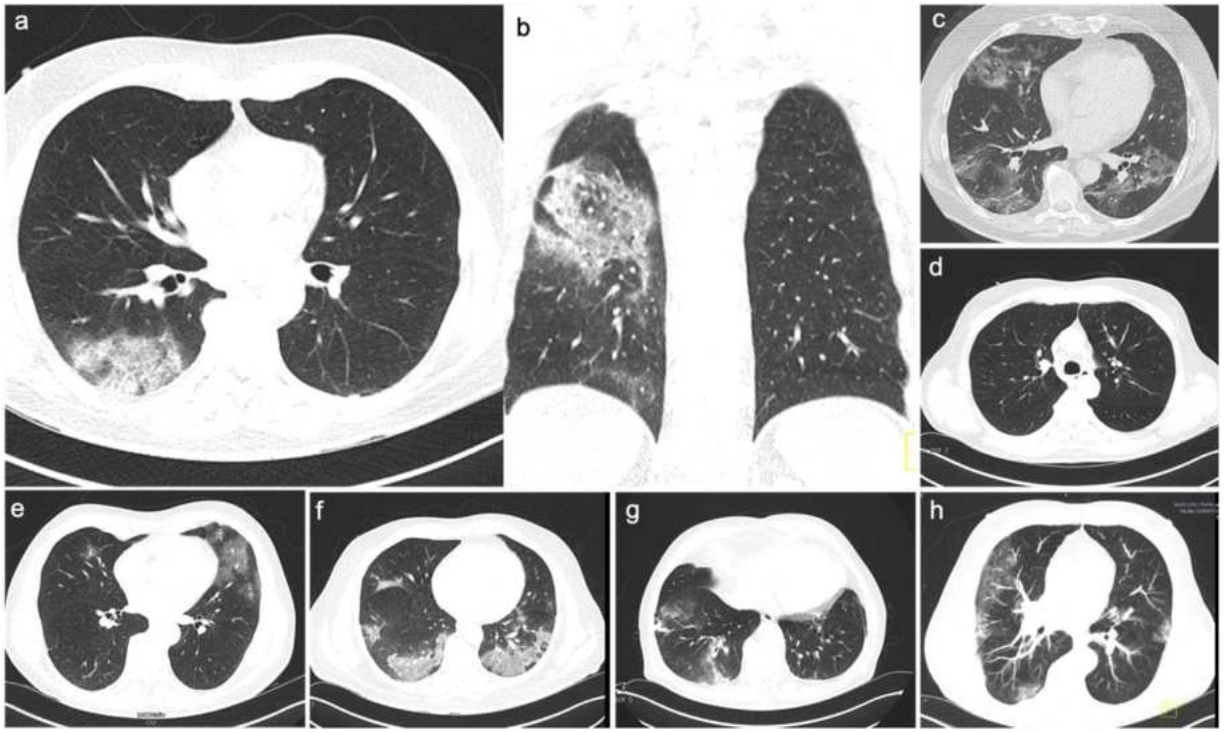


Fig. 1 – Lung imaging for all the patients. Computed tomography lung imaging was performed for all patients on admission (±5 d). All patients showed signs of viral pneumonia, as evidenced from the images. (A,B) Images for patient 1 in the coronal and axial planes. (C–H) Images for patients 2–7, respectively, in the coronal plane. Predominantly bilateral ground glass opacification and typical COVID19-associated crazy paving areas are evident (C,F,H).
COVID19 = coronavirus disease 2019.

absence of viral RNA in urine and the detection of SARS-CoV-2 in serum of two patients might indicate a role of infection in basal urothelial cells via blood that then causes cystitis. In addition, it has been postulated that endotheliitis might play a role in COVID-19 patients [4] and might contribute to local inflammation in the bladder (Fig. 2). Further evidence is urgently needed for a fuller understanding of the possible molecular mechanisms.

Table 3 – Pulmonary imaging and virological and laboratory results.

Test	Result
Atypical pneumonia on computed tomography, *n* (%)	7/7 (100)
SARS-CoV-2 RNA nasopharyngeal swab, *n* (%) [a]	7/7 (100)
SARS-CoV-2 RNA in serum, *n* (%) [a]	0/3 (0)
SARS-CoV-2 RNA in serum, *n* (%) [b]	2/4 (50)
SARS-CoV-2 RNA in urine, *n* (%)	0/6 (0)
Mean prostate volume, ml (range)	53 (35–66)
Mean residual urine, ml (range)	14.3 (0–40)
Mean urine osmolarity, mosm/kg (range) [a]	547.6 (383–702)
Mean prostate-specific antigen, ng/mL (range) [a]	1.47 (0.3–3.6)
Mean creatinine, mg/dl (range) [a]	0.92 (0.7–1.4)
Mean creatinine, mg/dl (range) [b]	0.87 (0.6–1.6)
Mean maximum IL-6, pg/mL (range)	215 (26.3–1086)
Mean procalcitonin, ng/mL (range) [a]	0.1 (>0.1–0.4)
Mean lactate dehydrogenase, U/l (range) [a]	334 (223–565)
Mean leukocytes, g/l (range) [a]	5.9 (2.8–9.7)
Mean neutrophils, % (range) [a]	64 (41–92)
Mean lymphocytes, % (range) [a]	18 (6–30)
Mean eosinophils, % (range) [a]	0.7 (<1–2)

[a] Day 0–5.
[b] Day 5–10.

2.2. *Clinical implications*

Classical symptoms of urinary tract infection or urosepsis such as fever and frequent urination might be misleading during the current COVID-19 pandemic. In general, diagnosis of COVID-19 is challenging as patients often present with unclear or even subclinical signs of disease [9]. Contaminated

Table 4 – Standard urinary analysis.

	Patients, *n* (%)
Urinary infection	0/7 (0)
Urine dipstick	
Negative for leukocytes	7/7 (100)
Urine sediment	
Negative for leukocytes	2/4 (50)
1–3 leukocytes per high-power field	2/4 (50)
Microhematuria	3/4 (75)
Urine cultures negative [a]	6/6 (100)

[a] Urine culture was not performed for one patient for whom the urine dipstick and urine sediment were negative for leukocytes.

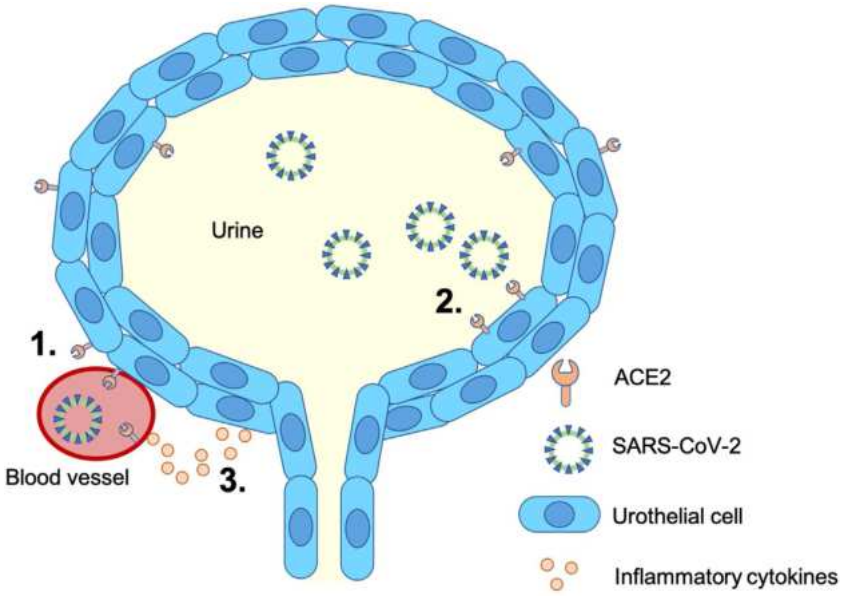


Fig. 2 – Potential mode of action. ACE2 has been described as the receptor for SARS-CoV-2, so urothelial cells might be affected in COVID-19 patients [6]. As localization of expression is unclear so far, basal or luminal expression is possible, so two possible infection routes could be hypothesized: (1) infection via capillaries is possible, especially in the light of viraemia an infection route of interest; (2) infection via urine might be possible, as SARS-CoV-2 has been detected in urine elsewhere [7]. (3) Alternatively, cystitis might be secondary due to local inflammation (eg, endotheliitis) [4]. ACE2 = angiotensin-converting enzyme 2; COVID19 = coronavirus disease 2019; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

urine samples may hamper accurate interpretation of urine diagnostics. Furthermore, urological patients often have ureteral stents or other prosthetic materials that can lead to infected sediments in urine analysis. As these patients are often elderly or immunocompromised with comorbidities such as cancer or diabetes, they represent a high-risk cohort for both urosepsis and severe COVID-19 disease. We therefore believe that in the current COVID-19 pandemic, laboratory work-up should include blood tests such as full blood count, interleukin-6, ferritin, procalcitonin, PSA (in males), and C-reactive protein, as well as urinary examination (microscopy and culture) and nasopharyngeal swab testing for SARS-CoV-2 RNA. These diagnostic tools may be critical for differentiation between COVID-19 and urological diagnoses in patients presenting with urinary frequency.

2.3. Conclusions

We identified higher urinary frequency as an additional symptom of SARS-CoV-2 infection independent of acute renal injury or urinary tract infection in a small series of hospitalized patients. Since urinary frequency along with clinical signs such as fever and positive laboratory results for inflammatory markers may be misinterpreted as urosepsis, knowledge of this finding is important for urologists during the current COVID-19 pandemic. Further research is warranted to understand the molecular mechanisms leading to urinary frequency, potentially attributed to viral cystitis in SARS-CoV-2–infected patients, and to determine its prognostic value.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: We thank all the patients for participating in our study and all the physicians, nurses, and staff involved in the management of COVID-19 patients. We are also grateful for the efforts of Johannes Hellmuth and the team involved in establishing the prospective COVID-19 register at LMU München for providing this research platform for the benefit of patients.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.05.013.

References

[1] World Health Organization. Coronavirus disease (COVID-2019) situation reports. World Health Organization Web site. www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[2] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
[3] Rocco B, Sighinolfi MC, Mussini C. COVID-19: importance of the awareness of the clinical syndrome by urologists. Eur Urol 2020;78:e40–1.
[4] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.
[5] Li W, Sui J, Huang IC, et al. The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. Virology 2007;367:367–74.
[6] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of

different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14:185–92. http://dx.doi.org/10.1007/s11684-020-0754-0.
[7] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
[8] Herold T., Jurinovic V., Arnreich C., et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv In press. www.medrxiv.org/content/10.1101/2020.04.01.20047381v2.
[9] Song JY, Yun JG, Noh JY, Cheong HJ, Kim WJ. Covid-19 in South Korea—challenges of subclinical manifestations. N Engl J Med 2020;382:1858–9.
[10] Guo L, Wei D, Zhang X, et al. Clinical features predicting mortality risk in patients with viral pneumonia: the MuLBSTA score. Front Microbiol 2019;10:275.

ischemia times for the cohort (MAC 17 min, SAC 15 min) can perfectly explain the lack of benefit of SAC or OC over MAC.

In our opinion, more evidence is needed regarding patients with CKD, ideally from randomized prospective trials in which renal function is assessed via precise methods such as scintigraphy. Results from such trials could inform about the best possible technique to minimize ischemia times and potentially reduce complications and blood loss. So far, it is clear that PN can be performed safely with MAC for patients with CKD as long as ischemia times are kept short.

Conflicts of interest: The author has nothing to disclose.

References

[1] Beksac AT, Okhawere KE, Rosen DC, et al. Do patients with stage 3–5 chronic kidney disease benefit from ischaemia-sparing techniques during partial nephrectomy? BJU Int 2019;125:442–8.
[2] Simone G, Gill IS, Mottrie A, et al. Indications, techniques, outcomes, and limitations for minimally ischemic and off-clamp partial nephrectomy: a systematic review of the literature. Eur Urol 2015;68:632–40.
[3] Scosyrev E, Messing EM, Sylvester R, et al. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014;65:372–7.
[4] Patel AR, Eggener SE. Warm ischemia less than 30 minutes is not necessarily safe during partial nephrectomy: every minute matters. Urol Oncol 2011;29:826–8.
[5] Porpiglia F, Bertolo R, Amparore D, et al. Evaluation of functional outcomes after laparoscopic partial nephrectomy using renal scintigraphy: clamped vs clampless technique. BJU Int 2015;115:606–12.

Diego M. Carrion*, Alfredo Aguilera Bazán, Luis Martínez-Piñeiro
Department of Urology, La Paz University Hospital, Autonomous University of Madrid, Madrid, Spain

*Corresponding author.
E-mail addresses: diegocarrionm@hotmail.com, diego.carrion@salud.madrid.org (D.M. Carrion).

Re: Adjuvant Chemotherapy in Upper Tract Urothelial Carcinoma (the POUT Trial): A Phase 3, Open-label, Randomised Controlled Trial

Birtle A, Johnson M, Chester J, et al

Lancet. In press. https://doi.org/10.1016/S0140-6736(20)30415-3

Experts' summary:

The authors report results from a randomised phase 3 trial investigating four cycles of chemotherapy with cisplatin or carboplatin plus gemcitabine versus surveillance in patients with locally advanced upper urinary tract carcinoma (UTUC; pT2–4 pN0/pT_{any} N1–3 M0) after nephroureterectomy. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), adverse events (AEs), and quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire. To detect a hazard ratio (HR) of 0.65 in favour of chemotherapy in an intention-to-treat analysis, 345 patients with 172 events were required. The trial stopped when the early stopping criterion for efficacy was met at a preplanned interim analysis with 261 patients included. At median follow-up of 30.3 mo, adjuvant chemotherapy significantly improved DFS (HR 0.45, 95% confidence interval [CI] 0.30–0.68; $p = 0.0001$) but results for OS are not yet available. The grade 3–4 AE rate was 44% in the treatment arm versus 4% in the surveillance arm. The authors conclude that adjuvant chemotherapy should be a new standard of care for this population.

Experts' comments:

Acknowledging differences between UTUC and transitional cell carcinoma of the bladder (TCC) [1], the conclusion from POUT requires caution in view of the EORTC 30994 immediate versus deferred chemotherapy trial following cystectomy for locally advanced TCC of the bladder [2]. Admittedly, in POUT, which did not require extended lymph-node dissection, 9% of patients had either pathological or radiological N1–3 disease, versus 70% in EORTC 30994. In the EORTC trial, which failed to recruit the 660 patients required, OS was the primary endpoint and was underpowered in the final analysis with 284 patients. However, we should remember that at threefold longer median follow-up than in POUT, four cycles of immediate adjuvant chemotherapy for TCC of the bladder (including cisplatin plus gemcitabine) significantly improved only progression-free survival (HR 0.54, 95% CI 0.4–0.73; $p < 0.0001$) and not OS (HR 0.78, 95% CI 0.56–1.08; $p = 0.13$) [2]. In addition, adjuvant trials base their DFS endpoint on radiological and not symptomatic recurrence [3]. In the POUT QoL analysis, patients in both arms had similar QoL at 12 mo ($p = 0.20$), suggesting no increase in symptomatic recurrences in the surveillance arm, while QoL dropped significantly in the first 6 mo in the chemotherapy arm ($p = 0.0028$). Routine use of UTUC adjuvant chemotherapy should be balanced against the high rate of grade 3–4 AEs, a currently unreported OS benefit, and unproved decrease in recurrence-related symptoms.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Audenet F, Isharwal S, Cha EK, et al. Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. Clin Cancer Res 2019;25:967–76.
[2] Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994):

an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015;16:76–86.
[3] Sun M, Marconi L, Eisen T, et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. Eur Urol 2018;74:611–20.

Teele Kuusk, Axel Bex*
Specialist Centre for Kidney Cancer, UCL Division of Surgery and Interventional Science, Royal Free London NHS Foundation Trust, London, UK

*Corresponding author. Specialist Centre for Kidney Cancer, UCL Division of Surgery and Interventional Science, Royal Free London NHS Foundation Trust, London NW3 2QG, UK.
E-mail address: a.bex@ucl.ac.uk (A. Bex).

Re: Improving Management of Upper Tract Urothelial Carcinoma

Tay LJ, Chatterton K, Colemeadow J, Nair R, Bultitude M, Thomas K

BJU Int. In press. https://doi.org/10.1111/bju.15068

Experts' summary:
The authors from Guy's Hospital report their patterns of care after streamlining their management of upper tract urothelial carcinomas (UTUC) by creating a multidisciplinary team (MDT) within the existing bladder MDT. For the first 32 patients in the new setting who were treated with definitive surgery, the median time from referral to surgery decreased from 54 to 33 d compared to the preceding 6-mo period. Furthermore, the proportion of patients treated with radical nephroureterectomy who had undergone a diagnostic ureteroscopy was only 46%, which contributed to more rapid booking of the patients who actually needed diagnostic ureteroscopy.

Experts' comments:
Several factors contribute to the suitability of an MDT in UTUC: the different additional diagnostic options (ureteroscopies, pyelographies, selective cytologies), the wide variety of treatment alternatives, and above all the rareness of the disease. In one survey [1], the urologic malignancy for which treatment changed most frequently (44%) after implementing an MDT approach was bladder cancer; considering the additional complexity of UTUC, at least the same proportion is likely for this disease entity. Furthermore, improving the interaction between urologists, nuclear medicine specialists, radiologists, oncologists, pathologists, specialist nurses, and clinical research representatives in the MDT setting will repeatedly give the opportunity to highlight and improve all components of the management of the disease. For example, considering the current diversity of computed tomography (CT) urogram techniques [2], reassessment of the CT urogram during the MDT evaluating the quality of the examination is likely to affect the use and type of additional diagnostic procedures. The higher risk of intravesical recurrence after diagnostic ureteroscopy before definitive surgery [3] must be balanced against diagnostic uncertainties when maximizing the diagnostic information from available urinary cytology specimens by applying the Paris System during reassessment of cytology specimens at the MDT [4]. At our center, where the MDT is similar to that described by Tay and coworkers, the rate of ureteroscopy before robot-assisted nephroureterectomy was 11/26 (42%) in 2019. With phase 3 trial data supporting adjuvant chemotherapy in advanced UTUC, there is a greater need to include preoperative assessment of increases in split renal function, especially in the setting of limited node-positive disease when preoperative induction chemotherapy is a treatment option. Furthermore, if suspicion of locally advanced disease is raised at an MDT, a nuclear medicine specialist might suggest a fluorodeoxyglucose positron emission tomography/CT on the basis of the recently reported high sensitivity and specificity for detection of nodal metastases with this modality in UTUC [5].

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: This work was supported by the Swedish Cancer Society (CAN 2017/278) and the Foundation of Urological Research (Ove and Carin Carlsson Bladder Cancer donation).

References

[1] Kurpad R, Kim W, Rathmell WK, et al. A multidisciplinary approach to the management of urologic malignancies: does it influence diagnostic and treatment decisions? Urol Oncol 2011;29:378–82.
[2] Shaish H. Making sense of the CT urogram. Eur Radiol 2020;30:1385–6.
[3] Chung Y, Lee DH, Lee M, et al. Impact of diagnostic ureteroscopy before radical nephroureterectomy on intravesical recurrence in patients with upper tract urothelial cancer. Investig Clin Urol 2020;61:158–65.
[4] McIntire PJ, Snow JT, Robinson BD, et al. Improved correlation of urinary cytology specimens using the Paris System in biopsy-proven upper tract urothelial carcinomas. Cancer Cytopathol 2018;126:498–504.
[5] Voskuilen CS, Schweitzer D, Jensen JB, et al. Diagnostic value of ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography for lymph node staging in patients with upper tract urothelial carcinoma. Eur Urol Oncol 2020;3:73–9.

Fredrik Liedberg[a,b,*], Anne Sörenby[a,b]
[a]*Institution of Translational Medicine, Lund University, Malmö, Sweden*
[b]*Department of Urology, Skåne University Hospital, Malmö, Sweden*

*Corresponding author. Department of Urology, Skåne University Hospital, Department of Translational Medicine, Lund University, Jan Waldenströms gata 7, SE-205 02 Malmö, Sweden.
E-mail address: fredrik.liedberg@med.lu.se (F. Liedberg).

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Words of Wisdom

Re: Do Patients with Stage 3–5 Chronic Kidney Disease Benefit from Ischaemia-sparing Techniques During Partial Nephrectomy?

Beksac AT, Okhawere KE, Rosen DC, et al

BJU Int 2020;125:442–8

Experts' summary:

In this multicenter, retrospective study, Beksac et al evaluated 462 patients with chronic kidney disease (CKD) who underwent robot-assisted partial nephrectomy (PN) between 2006 and 2018 to analyze whether modified clamping techniques could offer benefits for renal function in patients with stage 3–5 CKD [1]. Clamping techniques besides main arterial clamping (MAC) included selective arterial clamping (SAC) and off-clamp (OC), used in 48 (10.4%) and 39 patients (8.4%), respectively. Renal function was assessed as estimated glomerular filtration rate (eGFR), which was similar between the groups at baseline. Mean follow-up was 12 mo, and eGFR measurements at >24 mo were excluded to limit confounding variables on renal function. The groups differed in the following variables: MAC patients had higher body mass index (BMI) and were less likely to have hypertension, more likely to have a larger tumor, and more likely to have completely endophytic tumors. Conversely, tumors for which SAC was used were more likely to have a higher RENAL score, to be hilar, and in solitary kidneys.

In the multivariable analysis adjusted for BMI, hypertension, solitary kidney, tumor size, RENAL nephrometric score, endophytic tumors, laterality, and hilar, there were no differences between SAC and MAC or between OC and MAC in the decline in eGFR over time. The authors found that the complication rate, estimated blood loss, and operative time were similar for non-MAC and MAC patients, and that these techniques were not associated with any functional benefit in patients with stage 3–5 CKD.

Experts' comments:

The study by Beksac et al deals with a specific population never assessed before in terms of ischemia during PN, patients with stage 3–5 CKD. These results will further enrich the debate about the need for clamping techniques for the group of patients that we believe benefit the most from PN and modified clamping techniques. These results will further enrich the discussion over PN in this select group of patients with CKD.

The most relevant data probably come from the recent systematic review by Simone et al [2], who concluded that OC PN may be particularly applicable for patients presenting with low baseline renal function and maintains safety in terms of complications and negative surgical margins.

Doubts over the ideal strategy for preserving renal function arose after the only randomized clinical trial of PN versus radical nephrectomy, EORTC-30904. The study prompted a different view of PN, because the authors proved that although nephron-sparing surgery can substantially reduce the incidence of moderate renal dysfunction, this did not result in greater survival over median follow-up of 7.7 yr [3].

The fact that this retrospective series analyzed patients since 2006 helps us to interpret the results in a more contemporary fashion, mainly because other studies involve patients treated over a longer period of time, when anesthesia techniques and patient care were not as evolved. Although the study was retrospective, the groups were well balanced, mean baseline eGFR was similar, and most of the patients in all three groups had stage 3 CKD (93.6% for MAC, 100% for SAC, and 89.7% for OC).

Regarding the differences between the groups, as this was not a randomized trial and all surgeons had experience in the three techniques, we easily understand the use of specific techniques for some cases. MAC may be preferred in cases for which more bleeding is expected, such as larger and completely endophytic tumors. SAC would be preferred for solitary kidneys, for which surgeons will try to minimize ischemia to healthy parenchyma as much as possible. In the case of hilar tumors, as dissection is more precise within this area, it is theoretically easier to continue dissecting though arterial branches and perform selective clamping.

Minimization of renal function loss depends on the so-called three Qs: quality (renal function before surgery), quantity (renal parenchyma preserved during surgery), and quickness (ischemia time) [4]. Although larger tumors will involve greater loss of functional units within a kidney, in our opinion, minimizing ischemia time, regardless of clamping technique, is probably the most important of these three characteristics.

Porpiglia et al [5] assessed renal function postoperatively using renal scintigraphy and concluded that OC might not be necessary for most patients if the ischemia time is kept to <25 min. Thus, we agree with the authors that the low mean

https://doi.org/10.1016/j.eururo.2020.06.012

ischemia times for the cohort (MAC 17 min, SAC 15 min) can perfectly explain the lack of benefit of SAC or OC over MAC.

In our opinion, more evidence is needed regarding patients with CKD, ideally from randomized prospective trials in which renal function is assessed via precise methods such as scintigraphy. Results from such trials could inform about the best possible technique to minimize ischemia times and potentially reduce complications and blood loss. So far, it is clear that PN can be performed safely with MAC for patients with CKD as long as ischemia times are kept short.

Conflicts of interest: The author has nothing to disclose.

References

[1] Beksac AT, Okhawere KE, Rosen DC, et al. Do patients with stage 3–5 chronic kidney disease benefit from ischaemia-sparing techniques during partial nephrectomy? BJU Int 2019;125:442–8.
[2] Simone G, Gill IS, Mottrie A, et al. Indications, techniques, outcomes, and limitations for minimally ischemic and off-clamp partial nephrectomy: a systematic review of the literature. Eur Urol 2015;68:632–40.
[3] Scosyrev E, Messing EM, Sylvester R, et al. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014;65:372–7.
[4] Patel AR, Eggener SE. Warm ischemia less than 30 minutes is not necessarily safe during partial nephrectomy: every minute matters. Urol Oncol 2011;29:826–8.
[5] Porpiglia F, Bertolo R, Amparore D, et al. Evaluation of functional outcomes after laparoscopic partial nephrectomy using renal scintigraphy: clamped vs clampless technique. BJU Int 2015;115:606–12.

Diego M. Carrion*, Alfredo Aguilera Bazán, Luis Martínez-Piñeiro
Department of Urology, La Paz University Hospital, Autonomous University of Madrid, Madrid, Spain

*Corresponding author.
E-mail addresses: diegocarrionm@hotmail.com, diego.carrion@salud.madrid.org (D.M. Carrion).

Re: Adjuvant Chemotherapy in Upper Tract Urothelial Carcinoma (the POUT Trial): A Phase 3, Open-label, Randomised Controlled Trial

Birtle A, Johnson M, Chester J, et al

Lancet. In press. https://doi.org/10.1016/S0140-6736(20)30415-3

Experts' summary:

The authors report results from a randomised phase 3 trial investigating four cycles of chemotherapy with cisplatin or carboplatin plus gemcitabine versus surveillance in patients with locally advanced upper urinary tract carcinoma (UTUC; pT2–4 pN0/pT_{any} N1–3 M0) after nephroureterectomy. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), adverse events (AEs), and quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire. To detect a hazard ratio (HR) of 0.65 in favour of chemotherapy in an intention-to-treat analysis, 345 patients with 172 events were required. The trial stopped when the early stopping criterion for efficacy was met at a preplanned interim analysis with 261 patients included. At median follow-up of 30.3 mo, adjuvant chemotherapy significantly improved DFS (HR 0.45, 95% confidence interval [CI] 0.30–0.68; $p = 0.0001$) but results for OS are not yet available. The grade 3–4 AE rate was 44% in the treatment arm versus 4% in the surveillance arm. The authors conclude that adjuvant chemotherapy should be a new standard of care for this population.

Experts' comments:

Acknowledging differences between UTUC and transitional cell carcinoma of the bladder (TCC) [1], the conclusion from POUT requires caution in view of the EORTC 30994 immediate versus deferred chemotherapy trial following cystectomy for locally advanced TCC of the bladder [2]. Admittedly, in POUT, which did not require extended lymph-node dissection, 9% of patients had either pathological or radiological N1–3 disease, versus 70% in EORTC 30994. In the EORTC trial, which failed to recruit the 660 patients required, OS was the primary endpoint and was underpowered in the final analysis with 284 patients. However, we should remember that at threefold longer median follow-up than in POUT, four cycles of immediate adjuvant chemotherapy for TCC of the bladder (including cisplatin plus gemcitabine) significantly improved only progression-free survival (HR 0.54, 95% CI 0.4–0.73; $p < 0.0001$) and not OS (HR 0.78, 95% CI 0.56–1.08; $p = 0.13$) [2]. In addition, adjuvant trials base their DFS endpoint on radiological and not symptomatic recurrence [3]. In the POUT QoL analysis, patients in both arms had similar QoL at 12 mo ($p = 0.20$), suggesting no increase in symptomatic recurrences in the surveillance arm, while QoL dropped significantly in the first 6 mo in the chemotherapy arm ($p = 0.0028$). Routine use of UTUC adjuvant chemotherapy should be balanced against the high rate of grade 3–4 AEs, a currently unreported OS benefit, and unproved decrease in recurrence-related symptoms.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Audenet F, Isharwal S, Cha EK, et al. Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. Clin Cancer Res 2019;25:967–76.
[2] Sternberg CN, Skoneczna I, Kerst JM, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994):

Re: Prostate-specific Membrane Antigen PET-CT in Patients with High-risk Prostate Cancer Before Curative-intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multi-centre Study

Hofman MS, Lawrentschuk N, Francis RJ, et al

Lancet 2020;395:1209–16

Expert's summary:

In this randomised study, the authors compared the performance of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-computed tomography (CT) versus conventional imaging in 302 men with high-risk prostate cancer (prostate-specific antigen >20 ng/ml, grade group 3–5, clinical stage ≥ T3) [1]. The primary endpoint was the performance (patient-level analysis) of imaging for detecting either nodal or distant metastatic disease. PSMA PET-CT had a 27% absolute greater area under the receiver operating characteristic curve for accuracy than conventional imaging, and higher sensitivity (85% vs 38%) and specificity (98% vs 91%). The number of equivocal lesions was reduced by approximately three when PSMA PET-CT was used compared with conventional imaging. A clinical management change was considered in 15% of men undergoing conventional imaging after randomisation, compared with 28% in men undergoing PSMA PET-CT ($p = 0.008$).

Expert's comments:

Novel imaging tools such as PET-CT have been developed to more accurately detect disease with low metastatic burden and potentially modify cancer management and improve outcomes [2,3]. These assumptions are attributed to a higher tumour-to-background contrast and to the radiotracer specificity for prostate cancer cells. However, until this publication, firm prospective comparative data were missing in the context of preoperative assessment. This randomised trial confirms with a high level of evidence that PSMA PET-CT outperforms conventional imaging for detection of metastatic disease in the setting of presumably localised high-risk prostate cancer in men who are candidates for radical treatment of the primary tumour. It demonstrates that PSMA PET-CT can (or should) replace conventional imaging given its meaningful impact on treatment decision-making. The main limitation is that histological confirmation of metastatic tissue was not systematically achieved for all participants, even though biopsy of suspected sites was strongly encouraged in the protocol. Nevertheless, the authors included 6-mo repeat imaging to confirm or not the metastatic nature of equivocal lesions. On the basis of these findings, PSMA PET-CT undoubtedly improves the snapshot of high-risk disease. However, we do not really know to date if this improvement in detection leads to better disease management or better outcomes. One can argue that this high-resolution imaging, if positive, could lead to undertreatment of the primary tumour. Nevertheless, given the available literature on oligometastatic disease, the advent of PET-CT as a staging tool could improve the management of these patients at high risk of recurrence via early targeting of small metastatic lesions using stereotactic body radiotherapy and/or a more aggressive multimodal strategy [4,5].

Conflicts of interest: The author has nothing to disclose.

References

[1] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.

[2] Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2020;77:403–17.

[3] Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncol 2019;5:856–63.

[4] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66.

[5] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.

Guillaume Ploussard[a,*]

[a]*Department of Urology, La Croix du Sud Hospital, Quint Fonsegrives, France*

*Corresponding author: Department of Urology, La Croix du Sud Hospital, 52, chemin de Ribaute, Quint Fonsegrives, 31130, France

E-mail address: g.ploussard@gmail.com.

Re: Variability of the Positive Predictive Value of PI-RADS for Prostate MRI Across 26 Centers: Experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused Panel

Westphalen AC, McCulloch CE, Anaokar JM, et al

Radiology 2020;296:76–84

Experts' summary:

The Society of Abdominal Radiology Prostate Cancer Disease panel recently reported a retrospective, cross-sectional study evaluating the ability of prostate magnetic resonance imaging (MRI) to detect International Society of Urological Pathology (ISUP) grade group ≥2 (GG ≥ 2) cancer at multiple centres [1]. The study goal was to document variability in GG ≥ 2 cancer detection and provide a snapshot of MRI performance in mostly academic US centres. Data for a heterogeneous cohort of 3449 men with Prostate Imaging-Reporting and Data System (PI-RADS) from two to five lesions (biopsy-naïve 38%, prior biopsy with positive and negative histology 56%, unknown 6%) were analysed as a single pool. Concomitant systematic transrectal ultrasound-guided biopsy (SB) was

performed in 92%. The incidence of GG ≥ 2 cancers was 49% (Fig. 1).

The positive predictive value (PPV) variance by PI-RADS category was chosen as the measure for test performance. We believe that the report mistakenly ascribed the PPV variability observed to the PI-RADS assessment without considering multiple sources of heterogeneity.

Experts' comments:

MRI scans were evaluated by practice-based radiologists using PI-RADS assessment as part of standard clinical care [2]. The final report and not the MRI scans were reviewed. The authors failed to account for variables such as MR field strength, scanner vendor, endorectal coil use, image quality, reader quality, MRI positivity threshold for biopsy, biopsy-targeting method, experience of biopsy operators, need for SB samples, pathological expertise, or adherence to the ISUP consensus on Gleason grading [3]. The experience and biopsy performance of the 140 interpreting radiologists ($n = 89$) must inevitably vary across centres. The experience of the physicians performing biopsies and the radiological interactions for prostate and target delineations and ultrasound-MRI data fusion were not reported. Concomitant systematic biopsies were performed in most patients and analysed separately. Unfortunately, the expertise of the pathologists is also not described.

Three analyses were conducted: (1) model-based estimates of PPV at lesion level; (2) lesion-based intercentre PPV variability, evaluated as the median and interquartile range by PI-RADS category; and (3) patient-level benefits of the MRI pathway, compared in a subset undergoing both SB and targeted biopsies. The authors comment on two principal observations. First, men undergoing MRI-targeted biopsy demonstrate an overall low lesion-level PPV. Second, there is wide intercentre PPV variance regardless of the PI-RADS category cutoff used.

Lesion-level MRI pathway performance

PI-RADS assessment behaved properly, showing increasing rates of GG ≥ 2 cancers with increasing PI-RADS suspicion categories. The estimated PPV for PI-RADS assessment categories was 5% for PI-RADS 2, 15% for PI-RADS 3, 39% for PI-RADS 4, and 72% for PI-RADS 5. These data are in line with a recent meta-analysis by Barkovich et al [4].

Westphalen et al [1] emphasized the "low" lesion-level PPV (35%). There are two explanations for this seemingly "low" PPV. First, the case mix: the overall lesion PPV will be higher if more PI-RADS 4–5 findings are included and correspondingly will decrease with inclusion of more PI-RADS 2–3 lesions [5]. They included a high number of PI-RADS 2–3 lesions (40%), which automatically lowers the lesion-level PPV because of the lower prevalence of GG ≥ 2 cancers [1,4].

Second, PPV depends on disease prevalence in the study cohort. Some centres included men with prior positive biopsies with GG ≥ 2 cancers. It seems likely that urologists selected men for MRI-guided biopsy when they were uncertain about tumour grade. These lesions are likely to be smaller GG ≥ 2 cancers, which would reduce the PI-RADS 5 category and thus lower the PPV. These factors should have been mentioned as limitations if lesion-level PPV is adopted as a benchmark.

Intercentre lesion PPV variability

The authors noted wide intercentre lesion PPV variability. Multiple factors can affect the ability of the MRI pathway to detect GG ≥ 2. As mentioned, the leading issue is disease

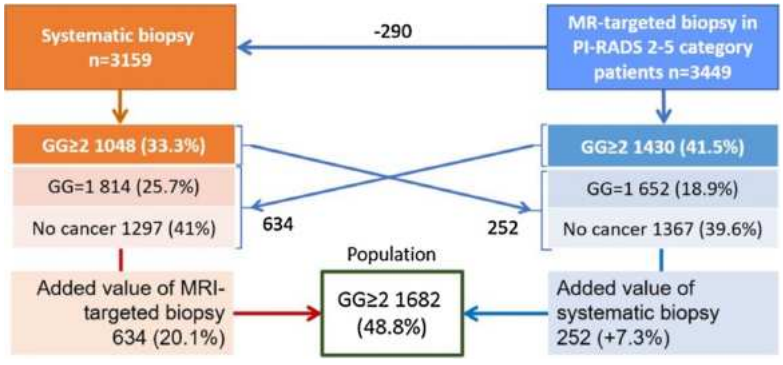


Fig. 1 – Patient flows and biopsy results for the study by Westphalen et al [1]. Only men undergoing targeted biopsies were analysed; 90% underwent systematic biopsies (selection criteria unknown), that is, 290 patients had only targeted biopsies.
GG = International Society of Urological Pathology grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System.

prevalence in the patient cohort. Statistical corrections in the study did not address the heterogeneous case mix at the centres (Fig. 2). As a result, the PPV for each centre differed. Furthermore, essential factors affecting the entire MRI pathway and thus the lesion PPV were not systematically considered [6–8]. There were no assessments of image quality, resulting in variable quality. The training and experience of the interpreting radiologists varied and are undocumented. Finally, there is likely to be wide inter-rater variability for GG scoring [9].

MRI pathway performance

The authors expressed concerns regarding the reliability of PI-RADS because of the high intercentre PPV variability. However, it is important to emphasise that the most important benefit of prostate MRI for biopsy-naïve men is its high patient-level negative predictive value (NPV) for GG > 2 cancers, rather than its lesion-based PPV. A high patient-level NPV allows biopsy avoidance in a substantial percentage of men and reduces the rate of detection of GG 1 cancer [10]. In this study we cannot estimate the patient-level variability of NPV because negative cases were not submitted for the review process.

Table 1 – Steps to achieving end-to-end quality in the MRI prostate cancer diagnostic pathway.[a]

Element	Comments
Patients	Risk-based selection
MRI data acquisition	Quality assurance and quality control of MRI machines, PI-RADS standard compliance, technologist expertise
MRI reading	Experienced readers
Selection for biopsy	Multidisciplinary team
Prebiopsy preparations	Prostate gland and target delineations and MRI-US data fusion
MRI-targeted biopsies	Skilled operators
Histopathology	Experienced pathologists

MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; US = ultrasound.
[a] Multiple elements must be coordinated for successful use of MRI for prostate cancer diagnosis. Diagnostic units require quality assurance programs, quality control of MRI and pathology evaluations, and trained individuals working within multidisciplinary teams.

Unlike the PPV, the NPV is less susceptible to operator biopsy performance and histopathological errors. Interestingly, the value of adding MRI biopsy to SB was high (20.1%; Fig. 1) compared to the Cochrane meta-analysis (10.9%) [11].

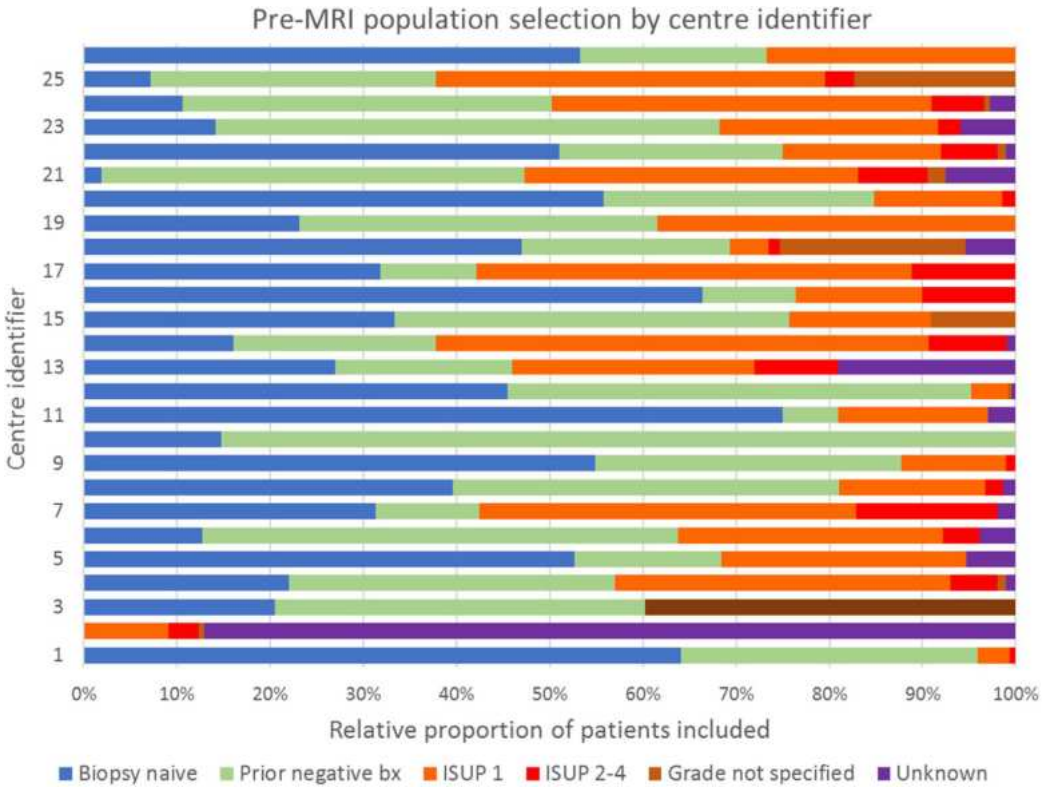


Fig. 2 – Heterogeneity in patient case mix at each centre. The case mix at participating centres was very heterogeneous, resulting in differing prevalence according to the proportion of each patient group included.
ISUP = International Society of Urological Pathology.

Conclusions

The title and take-home messages from the paper by Westphalen et al [1] may give a false impression that PI-RADS assessments appear to be underperforming. It is incorrect to suggest that the wide intercentre PPV indicates poor PI-RADS performance. Careful analysis of the data shows that the PI-RADS assessment performs well, as designed. The known patient benefits of MRI for detecting GG $\geq$ 2 cancers over SB are observable, even in this heterogeneous cohort. It must be emphasized again that the clinical benefits of the MRI pathway arise from its high patient-level NPV and not the PPV, which allows biopsy avoidance and reduces the detection rate of GG 1 cancer.

The PPV shows considerable intercentre variability caused by heterogeneities across the entire MRI pathway, from patient selection to MR image quality, to reading quality, to biopsy performance and pathological experience. It is essential to ensure that all individuals involved in the MRI pathway workflow are competent, and that quality controls and quality assurance procedures are in place at prostate MRI facilities (Table 1). The most important lesson from this paper is the high intercentre PPV variability, which clearly indicates the constant need to improve end-to-end quality in the MRI-directed diagnostic process.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Westphalen AC, et al. Variability of the positive predictive value of PI-RADS for prostate MRI across 26 centers: experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused Panel. Radiology 2020;296:76–84.

[2] Weinreb JC, et al. PI-RADS Prostate Imaging-Reporting and Data System: 2015, version 2. Eur Urol 2016;69:16–40.

[3] Epstein JI, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.

[4] Barkovich EJ, et al. A systematic review of the existing Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) literature and subset meta-analysis of PI-RADSv2 categories stratified by Gleason scores. Am J Roentgenol 2019;212:847–54.

[5] Moldovan PC, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol 2017;72:250–66.

[6] Kasabwala K, et al. The learning curve for magnetic resonance imaging/ultrasound fusion-guided prostate biopsy. Eur Urol Oncol 2019;2:135–40.

[7] Gordetsky JB, et al. MRI-targeted prostate biopsy: key considerations for pathologists. Histopathology. In press. https://doi.org/10.1111/his.14113.

[8] Gaziev G, et al. Defining the learning curve for multiparametric magnetic resonance imaging (MRI) of the prostate using MRI-transrectal ultrasonography (TRUS) fusion-guided transperineal prostate biopsies as a validation tool. BJU Int 2016;117:80–6.

[9] Shah MD, et al. Impact of the pathologist on prostate biopsy diagnosis and immunohistochemical stain usage within a single institution. Am J Clin Pathol 2017;148:494–501.

[10] Padhani AR, et al. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 status update and future directions. Eur Urol 2018;75:385–96.

[11] Drost F-JH, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol 2020;77:78–94.

[12] Ahdoot M, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917–28.

Anwar R. Padhani[a], Jelle Barentsz[b,*], Jeffrey Weinreb[c], Ivo Schoots[d], Clare Tempany[e]

[a]*Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, UK*

[b]*Department of Radiology, Nuclear Medicine, and Anatomy, Radboud University Medical Center, Nijmegen, The Netherlands*

[c]*Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT, USA*

[d]*Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands*

[e]*Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA*

*Corresponding author. Department of Radiology, Nuclear Medicine, and Anatomy, Radboud University Medical Center, Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail address: jelle.barentsz@radboudumc.nl (J. Barentsz).

https://doi.org/10.1016/j.euo.2018.07.005

Re: Prostate-specific Membrane Antigen PET-CT in Patients with High-risk Prostate Cancer Before Curative-intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multi-centre Study

Hofman MS, Lawrentschuk N, Francis RJ, et al

Lancet 2020;395:1209–16

Expert's summary:

In this randomised study, the authors compared the performance of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-computed tomography (CT) versus conventional imaging in 302 men with high-risk prostate cancer (prostate-specific antigen >20 ng/ml, grade group 3–5, clinical stage ≥ T3) [1]. The primary endpoint was the performance (patient-level analysis) of imaging for detecting either nodal or distant metastatic disease. PSMA PET-CT had a 27% absolute greater area under the receiver operating characteristic curve for accuracy than conventional imaging, and higher sensitivity (85% vs 38%) and specificity (98% vs 91%). The number of equivocal lesions was reduced by approximately three when PSMA PET-CT was used compared with conventional imaging. A clinical management change was considered in 15% of men undergoing conventional imaging after randomisation, compared with 28% in men undergoing PSMA PET-CT ($p = 0.008$).

Expert's comments:

Novel imaging tools such as PET-CT have been developed to more accurately detect disease with low metastatic burden and potentially modify cancer management and improve outcomes [2,3]. These assumptions are attributed to a higher tumour-to-background contrast and to the radiotracer specificity for prostate cancer cells. However, until this publication, firm prospective comparative data were missing in the context of preoperative assessment. This randomised trial confirms with a high level of evidence that PSMA PET-CT outperforms conventional imaging for detection of metastatic disease in the setting of presumably localised high-risk prostate cancer in men who are candidates for radical treatment of the primary tumour. It demonstrates that PSMA PET-CT can (or should) replace conventional imaging given its meaningful impact on treatment decision-making. The main limitation is that histological confirmation of metastatic tissue was not systematically achieved for all participants, even though biopsy of suspected sites was strongly encouraged in the protocol. Nevertheless, the authors included 6-mo repeat imaging to confirm or not the metastatic nature of equivocal lesions. On the basis of these findings, PSMA PET-CT undoubtedly improves the snapshot of high-risk disease. However, we do not really know to date if this improvement in detection leads to better disease management or better outcomes. One can argue that this high-resolution imaging, if positive, could lead to undertreatment of the primary tumour. Nevertheless, given the available literature on oligometastatic disease, the advent of PET-CT as a staging tool could improve the management of these patients at high risk of recurrence via early targeting of small metastatic lesions using stereotactic body radiotherapy and/or a more aggressive multimodal strategy [4,5].

Conflicts of interest: The author has nothing to disclose.

References

[1] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.

[2] Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2020;77:403–17.

[3] Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncol 2019;5:856–63.

[4] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66.

[5] Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.

Guillaume Ploussard[a,*]

[a]*Department of Urology, La Croix du Sud Hospital, Quint Fonsegrives, France*

*Corresponding author: Department of Urology, La Croix du Sud Hospital, 52, chemin de Ribaute, Quint Fonsegrives, 31130, France

E-mail address: g.ploussard@gmail.com.

Re: Variability of the Positive Predictive Value of PI-RADS for Prostate MRI Across 26 Centers: Experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused Panel

Westphalen AC, McCulloch CE, Anaokar JM, et al

Radiology 2020;296:76–84

Experts' summary:

The Society of Abdominal Radiology Prostate Cancer Disease panel recently reported a retrospective, cross-sectional study evaluating the ability of prostate magnetic resonance imaging (MRI) to detect International Society of Urological Pathology (ISUP) grade group ≥2 (GG ≥ 2) cancer at multiple centres [1]. The study goal was to document variability in GG ≥ 2 cancer detection and provide a snapshot of MRI performance in mostly academic US centres. Data for a heterogeneous cohort of 3449 men with Prostate Imaging-Reporting and Data System (PI-RADS) from two to five lesions (biopsy-naïve 38%, prior biopsy with positive and negative histology 56%, unknown 6%) were analysed as a single pool. Concomitant systematic transrectal ultrasound-guided biopsy (SB) was

an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 2015;16:76–86.
[3] Sun M, Marconi L, Eisen T, et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. Eur Urol 2018;74:611–20.

Teele Kuusk, Axel Bex*
Specialist Centre for Kidney Cancer, UCL Division of Surgery and Interventional Science, Royal Free London NHS Foundation Trust, London, UK

*Corresponding author. Specialist Centre for Kidney Cancer, UCL Division of Surgery and Interventional Science, Royal Free London NHS Foundation Trust, London NW3 2QG, UK.
E-mail address: a.bex@ucl.ac.uk (A. Bex).

Re: Improving Management of Upper Tract Urothelial Carcinoma

Tay LJ, Chatterton K, Colemeadow J, Nair R, Bultitude M, Thomas K

BJU Int. In press. https://doi.org/10.1111/bju.15068

Experts' summary:
The authors from Guy's Hospital report their patterns of care after streamlining their management of upper tract urothelial carcinomas (UTUC) by creating a multidisciplinary team (MDT) within the existing bladder MDT. For the first 32 patients in the new setting who were treated with definitive surgery, the median time from referral to surgery decreased from 54 to 33 d compared to the preceding 6-mo period. Furthermore, the proportion of patients treated with radical nephroureterectomy who had undergone a diagnostic ureteroscopy was only 46%, which contributed to more rapid booking of the patients who actually needed diagnostic ureteroscopy.

Experts' comments:
Several factors contribute to the suitability of an MDT in UTUC: the different additional diagnostic options (ureteroscopies, pyelographies, selective cytologies), the wide variety of treatment alternatives, and above all the rareness of the disease. In one survey [1], the urologic malignancy for which treatment changed most frequently (44%) after implementing an MDT approach was bladder cancer; considering the additional complexity of UTUC, at least the same proportion is likely for this disease entity. Furthermore, improving the interaction between urologists, nuclear medicine specialists, radiologists, oncologists, pathologists, specialist nurses, and clinical research representatives in the MDT setting will repeatedly give the opportunity to highlight and improve all components of the management of the disease. For example, considering the current diversity of computed tomography (CT) urogram techniques [2], reassessment of the CT urogram during the MDT evaluating the quality of the examination is likely to affect the use and type of additional diagnostic procedures. The higher risk of intravesical recurrence after diagnostic ureteroscopy before definitive surgery [3] must be balanced against diagnostic uncertainties when maximizing the diagnostic information from available urinary cytology specimens by applying the Paris System during reassessment of cytology specimens at the MDT [4]. At our center, where the MDT is similar to that described by Tay and coworkers, the rate of ureteroscopy before robot-assisted nephroureterectomy was 11/26 (42%) in 2019. With phase 3 trial data supporting adjuvant chemotherapy in advanced UTUC, there is a greater need to include preoperative assessment of increases in split renal function, especially in the setting of limited node-positive disease when preoperative induction chemotherapy is a treatment option. Furthermore, if suspicion of locally advanced disease is raised at an MDT, a nuclear medicine specialist might suggest a fluorodeoxyglucose positron emission tomography/CT on the basis of the recently reported high sensitivity and specificity for detection of nodal metastases with this modality in UTUC [5].

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: This work was supported by the Swedish Cancer Society (CAN 2017/278) and the Foundation of Urological Research (Ove and Carin Carlsson Bladder Cancer donation).

References

[1] Kurpad R, Kim W, Rathmell WK, et al. A multidisciplinary approach to the management of urologic malignancies: does it influence diagnostic and treatment decisions? Urol Oncol 2011;29:378–82.
[2] Shaish H. Making sense of the CT urogram. Eur Radiol 2020;30:1385–6.
[3] Chung Y, Lee DH, Lee M, et al. Impact of diagnostic ureteroscopy before radical nephroureterectomy on intravesical recurrence in patients with upper tract urothelial cancer. Investig Clin Urol 2020;61:158–65.
[4] McIntire PJ, Snow JT, Robinson BD, et al. Improved correlation of urinary cytology specimens using the Paris System in biopsy-proven upper tract urothelial carcinomas. Cancer Cytopathol 2018;126:498–504.
[5] Voskuilen CS, Schweitzer D, Jensen JB, et al. Diagnostic value of ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography for lymph node staging in patients with upper tract urothelial carcinoma. Eur Urol Oncol 2020;3:73–9.

Fredrik Liedberg[a,b,*], Anne Sörenby[a,b]
[a]*Institution of Translational Medicine, Lund University, Malmö, Sweden*
[b]*Department of Urology, Skåne University Hospital, Malmö, Sweden*

*Corresponding author. Department of Urology, Skåne University Hospital, Department of Translational Medicine, Lund University, Jan Waldenströms gata 7, SE-205 02 Malmö, Sweden.
E-mail address: fredrik.liedberg@med.lu.se (F. Liedberg).

Re: 17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort
Lin DW, Zheng Y, McKenney JK, et al

J Clin Oncol 2020;38:1549–57

Expert's summary:
Lin and colleagues evaluated the 17-gene Oncotype DX Genomic Prostate Score (GPS) test applied to diagnostic biopsy tissue from patients with low-risk prostate cancer. The test was evaluated as a predictor of adverse pathology (AP) in men who underwent radical prostatectomy after initial management with active surveillance (AS) [1]. In a multicenter setting, the authors also looked at the association between GPS and time to upgrading on surveillance biopsy. Among 432 men on AS with median follow-up of 4.6 yr, 167 (39%) showed upgrading at a subsequent biopsy. At a median of 2.1 yr after their diagnostic biopsy, 101 men (23%) underwent radical prostatectomy, of whom 51% showed AP. GPS was found to be associated with AP when the diagnostic Gleason grade group (GG) was taken into account, but not after adjustment for both prostate-specific antigen density (PSAD) and diagnostic GG. Interestingly, PSAD was significantly associated with AP. The authors concluded that GPS was significantly associated with AP in radical prostatectomy specimens when adjusted for diagnostic GG, but adding GPS to a model containing PSAD and diagnostic GG did not significantly improve stratification of risk for AP over the clinical variables alone. PSAD and percentage positive biopsy cores remained significantly associated with upgrading.

Expert's comments:
The value of adding a molecular test to clinical variables for risk stratification for patients with prostate cancer has been demonstrated in several studies. Four different tests are frequently used in the USA as they are covered by Medicare for qualified patients and mentioned in the latest National Comprehensive Cancer Network guidelines (v2.2019) [2]. An American Society of Clinical Oncology (ASCO)-European Association of Urology (EAU)-American Urological Association (AUA) multidisciplinary expert panel recently published guidelines on molecular biomarkers in localized prostate cancer and agreed that tissue-based molecular biomarkers may improve risk stratification when added to standard clinical parameters. However, the panel endorsed their use only in situations in which the assay results may have an impact on clinical decision-making [3]. In most studies, molecular markers have been evaluated for possible improvement in risk stratification and patient management. The use of molecular markers to predict disease progression in patients on AS has not been fully explored. The 17-gene Oncotype DX GPS test of diagnostic biopsy tissue has been shown to predict AP in patients with low- and intermediate-risk prostate cancer treated with immediate radical prostatectomy [4]. The test has also been externally validated [5].

There are many aspects on the use of tissue biomarkers for prostate cancer patients on AS. We are already using biomarkers to select patients suitable for AS. However, there are other biomarkers besides the costly molecular test. In the guidelines from the ASCO-EAU-AUA expert panel, the price for the most common molecular tests were between US$3900 and US$5150.

In the recent paper by Lin et al [1], PSAD and GG seemed to perform better than GPS in predicting AP. The value of GPS in predicting AP in men on AS was also evaluated by Kornberg et al [6]. In a single-center study involving 215 men, the authors found—in contrast to Lin et al—that GPS was an independent predictor of AP, with a statistically significant hazard ratio. The studies were not identically designed and there is a need for additional studies on the true value of molecular tissue biomarkers for men on AS for prostate cancer.

Another important aspect of the GPS test and other molecular biomarkers is the quality of the tissue samples analyzed. Besides the heavily discussed issue of intra- and intertumoral heterogeneity, there may be a problem with retrieval of sufficient RNA. The use of optimized processing protocols has not yet overcome this problem. In the study by Lin et al, 27% of the biopsies had insufficient residual tumor tissue for GPS testing, which represents a potential limitation of some tissue-based genomic assays.

Multiparametric magnetic resonance imaging may also play an important role in the optimization of surveillance schedules and triggers for intervention, and the same is true for germline DNA testing.

The multicenter study by Lin et al showed that GPS added to a model containing PSAD and diagnostic GG did not significantly improve stratification of risk for AP over the clinical variables alone. This is in line with the recent recommendations from the ASCO-EAU-AUA expert panel that tissue-based molecular tests should be used together with routine clinical factors and only in situations in which the results are likely to affect a clinical decision.

Conflicts of interest: The author has nothing to disclose.

References

[1] Lin DW, Zheng Y, McKenney JK, et al. 17-Gene genomic prostate score test results in the Canary Prostate Active Surveillance Study (PASS) Cohort. J Clin Oncol 2020;38:1549–57.
[2] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guideline in oncology. J Natl Compr Canc Netw 2019;17:479–505.
[3] Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular biomarkers on localized prostate cancer: ASCO guideline. J Clin Oncol 2019JCO1902768.
[4] Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550–60.
[5] Eggener SE, Karsh LI, Richardson T, et al. A 17-gene panel for prediction of adverse prostate cancer pathologic features: prospective clinical validation and utility. Urology 2019;126:76–82.
[6] Kornberg Z, Cooperberg MR, Cowan JE, et al. A 17-gene Genomic Prostate Score as a predictor of adverse pathology for men on active surveillance. J Urol 2019;202:702–9.

Anders S. Bjartell*
Department of Urology, Skåne University Hospital, Malmö, Sweden

*Department of Urology, Skåne University Hospital, Malmö, Sweden.
E-mail address: anders.bjartell@med.lu.se.

lifestyle modification, and different treatment regimens for this group.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: This study was supported by funding for C.D.F. from the University Hospital of Zurich and medAlumni Zurich, Stiftung für urologische Forschung, Marlis Geiser-Lemken Stiftung, Fonds zur Förderung des akademischen Nachwuchses, Ernst Göhner Stiftung, a SAKK/Dr. Paul Janssen Fellowship, and Arnold U. und Susanne Huggenberger-Bischoff Stiftung zur Krebsforschung; and for L.A.M. from the National Institutes of Health (U01 CA167552), the US Army Prostate Cancer Research Program (Idea Development Award PC060389, an Early-Investigator Research Award (W81XWH-18-1-0330), and Dana-Farber/Harvard Cancer Center Prostate SPORE Career Development Award (NIH/NCI P50 CA090381). L.A.M., K.L.P., K.H.S., and M.A.P. are Young Investigators of the Prostate Cancer Foundation. The funding bodies had no influence on the design or conduct of the study, analysis and interpretation of the data, or preparation of the article. We are grateful to the participants and staff of the Health Professionals Follow-up Study for their valuable contributions. We also thank the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nevada, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.05.035.

References

[1] Mahal BA, Yang DD, Wang NQ, et al. Clinical and genomic characterization of low–prostate-specific antigen, high-grade prostate cancer. Eur Urol 2018;74:146–54.
[2] Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol 2009;27:3459–64.
[3] Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. Nat Med 2017;23:664.

[a]*Department of Urology, University Hospital Zurich, University of Zurich, Zurich, Switzerland*
[b]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[c]*Department of Urology, The Christie and Salford Royal NHS Foundation Trusts, Manchester, UK*
[d]*Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[e]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[f]*Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna School of Medicine, Bologna, Italy*
[g]*Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA*
[h]*Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[i]*McGraw/Patterson Center for Population Sciences, Boston, MA, USA*
[j]*Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, USA*
[k]*Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

*Corresponding author. Department of Urology, University Hospital of Zurich, University of Zurich, Frauenklinikstrasse 10, Zurich 8091, Switzerland. Tel. +41 44 2551111.
E-mail address: christian.fankhauser@usz.chf (C.D. Fankhauser).

Elucidating Durable Responses to Immune Checkpoint Inhibition

Pasquale Rescigno [a,b], Caterina Aversa [a], Mateus Crespo [a], George Seed [a], Maryou Lambros [a], Bora Gurel [a], Ines Figueiredo [a], Diletta Bianchini [b], Ruth Riisnaes [a], Rita Pereira [a], Maria D. Fenor de la Maza [a,b], Juliet Carmichael [a,b], Khobe Chandran [b], Ana Ferreira [a], Claudia Bertan [a], Alec Paschalis [a,b], Andra Curcean [b], Adam Sharp [a,b], Wei Yuan [a], Nina Tunariu [a,b], Christian Poehlein [c], Suzanne Carreira [a], Johann S. de Bono [a,b,]*

Immune checkpoint inhibitors (ICIs) are under investigation for metastatic castration-resistant prostate cancer (mCRPC) [1]. Mismatch DNA repair deficiency (MMRd) [2] and high tumour lymphocyte infiltration (TIL) [3] represent biomarkers of ICI response. Here we report on two mCRPC patients with exceptional responses to pembrolizumab, outlining their disease biology in attempts to explain this sensitivity (previous oncological history is reported in the Supplementary material).

In November 2016, patient 1 started pembrolizumab 200 mg every 3 wk, when his baseline prostate-specific antigen (PSA) was 59 μg/l and scans showed a right external iliac nodal mass (Fig. 1A). The main adverse events were grade 4 hyperamylasaemia and grade 2 sicca syndrome, requiring a treatment break and high-dose steroids. He experienced a complete radiological response, with undetectable PSA, which persists 40 mo after starting pembrolizumab (Fig. 1B,C). Immunohistochemistry (IHC) studies were positive for

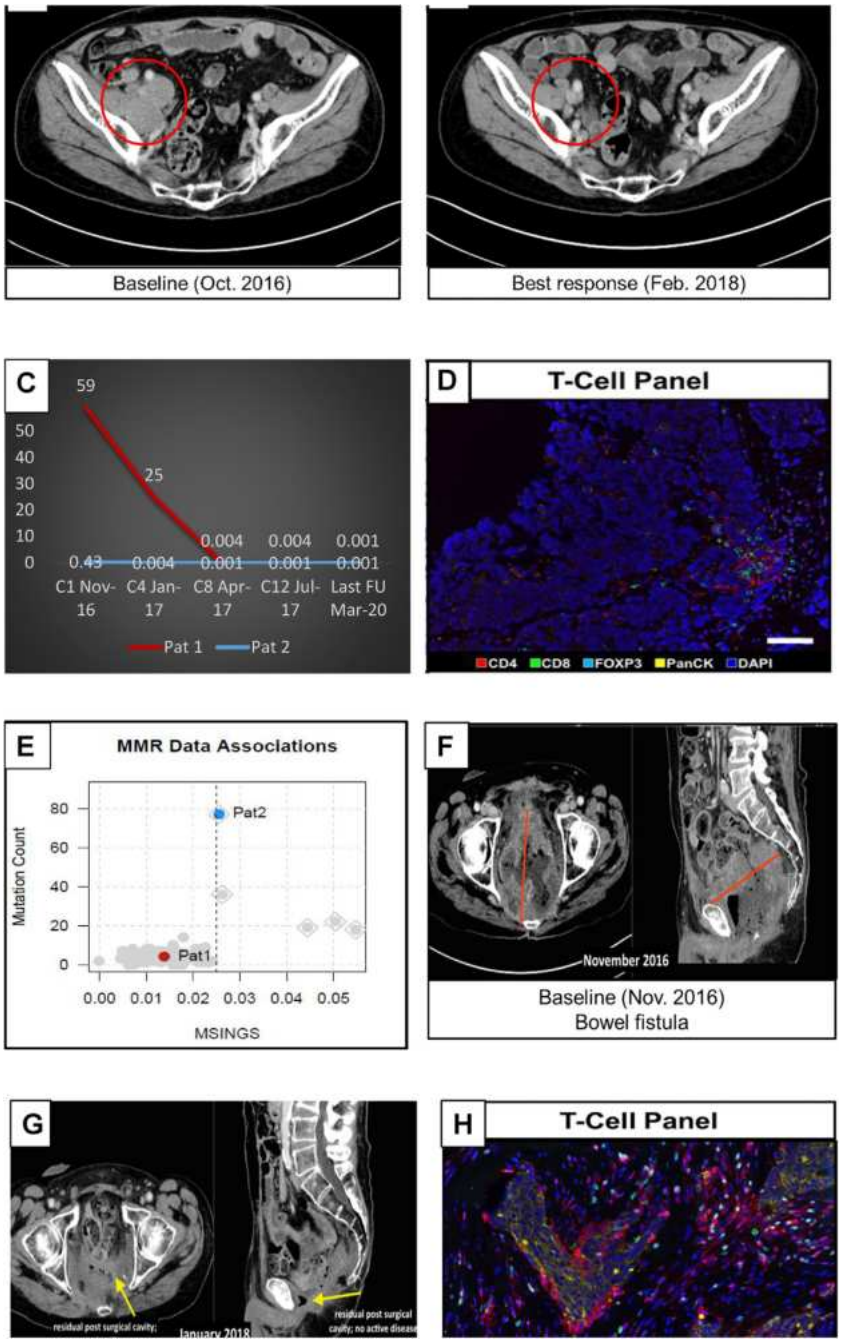


Fig. 1 – (A) Computed tomography (CT) scan at baseline before starting pembrolizumab in October 2016 depicting a right-sided internal iliac nodal mass measuring 33 mm. (B) CT scan in February 2018 after 20 courses of pembrolizumab depicting response. (C) Prostate-specific antigen during treatment and at last follow-up (FU) for patients 1 (red) and 2 (blue). (D) Multispectral, multicolour immunofluorescence depicting T-cell infiltration in a lymph node biopsy for patient 1. Red denotes $CD4^+$ cells, green, $CD8^+$ cells, and light blue, $FOXP3^+$ cells; this panel depicts few immune cells in this sample. (E) Scatter plot depicting mutation load versus microsatellite instability by next-generation sequencing (MSINGS) for 100 fresh biopsies from a Royal Marsden cohort. The red dot represents patient 1 and the blue dot, patient 2. Diamond frames indicate mismatch DNA repair (MMR) loss cases on immunohistochemistry. (F) CT scan for patient 2 before the start of pembrolizumab in November 2016 depicting a large pelvic mass with associated fistula. (G) Whole-body diffusion magnetic resonance imaging (MRI) scan in Jan 2018 showing the post-surgery pelvic cavity with no residual malignancy. (H) Multispectral, multicolour immunofluorescence for T-cell infiltration in a pelvic mass sample from patient 2 showing abundant infiltration of $CD4^+$ and $FOXP3^+$ cells.

MSH6, MSH2, MLH1, and PMS2, and negative for PD-L1, with a C-terminal binding antibody. IHC for $CD3^+$ and multicolour immunofluorescence analyses revealed few TILs (Fig. 1D). Next-generation sequencing (NGS) and copy number analyses showed ERCC2, ERCC3, FANCA, and TP53 deep deletions, with a low microsatellite instability (MSI)-NGS score and low mutation load (MutLoad) (Fig. 1E). Surprisingly, array-based comparative genomic hybridisation analysis detected a rearrangement in chromosome 9p between PD-L1 and PD-L2 with deletion of the 3′-untranslated region of PD-L1.

Patient 2 commenced pembrolizumab 200 mg every 3 wk in November 2016; his PSA was 0.43 μg/l and scans revealed bilateral pelvic nodes, a large pelvic mass (53 mm), and a complex fistula between the rectum and bladder. He received 11 pembrolizumab courses with no immunological toxicity and experienced a partial response. However, pembrolizumab was stopped because of fistula worsening requiring intravenous antibiotics and surgical intervention. He made a full recovery and remains disease-free 40 mo after starting pembrolizumab (Fig. 1F,G). Tumour NGS had indicated an MSH6 mutation (Y214*), high MutLoad, and high MSINGS score, with MSH6 loss but incomplete MSH2 loss on IHC, as well as PD-L1 positivity (1%). IHC showed high TILs; most of these cells were $CD4^+$FOXP3 and Tregs ($CD4^+FOXP3^+$; Fig. 1H).

We previously showed that a small but important subset of mCRPC tumours have evidence of MMRd by IHC and this is associated with high MutLoad and MSI-NGS. However, only some MMRd cancers present with high T-cell infiltration, PD-L1 protein expression, and elevated T-cell–associated transcripts [2].

The rearrangement identified for patient 1 was associated with immune evasion and PD-L1 overexpression in mouse models using an N-terminal binding antibody [4]. This could explain his PD-L1 negativity (since the antibodies routinely used target the C-terminus) and extraordinary response to pembrolizumab in an otherwise immune "cold" tumour.

Patient 2, besides MMRd, presented with a highly inflamed cancer, mainly represented by Tregs and $CD4^+$FOXP3 cells. Interestingly, in mCRPC models, ICIs reprogram $CD4^+$ cells towards a Th1 rather than Th17 lineage in nodal disease, possibly explaining this responsiveness [5].

In conclusion, elucidation of the mCRPC subset benefiting from ICIs requires multiple orthogonal assays, including genomic analyses, IHC, and tumour microenvironment studies.

Conflicts of interest: Johann S. de Bono has served on advisory boards for MSD, Merck Serono, Pfizer, Genentech/Roche, AstraZeneca, Astellas, Janssen, GSK, Genmab, Amgen, Daiichi Sankyo, and Bayer. The remaining authors have nothing to disclose.

Acknowledgements: Christian Poehlein is an employee of Merck Sharp&Dohme. Pasquale Rescigno is supported by a Prostate Cancer Foundation (PCF) Young Investigator Award.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.056.

References

[1] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395–405.

[2] Rodrigues DN, Rescigno P, Liu D, et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest 2018;128:4441–53.

[3] Daud AI, Loo K, Pauli ML, et al. Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma. J Clin Invest 2016;126:3447–52.

[4] Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. Nature 2016;534:402–6.

[5] Jiao S, Subudhi SK, Aparicio A, et al. Differences in tumor microenvironment dictate T helper lineage polarization and response to immune checkpoint therapy. Cell 2019;179, 1177–90.e13.

[a]*The Institute of Cancer Research, London, UK*
[b]*The Royal Marsden Hospital, London, UK*
[c]*Merck & Co., Kenilworth, NJ, USA*

*Corresponding author. The Institute of Cancer Research, 123 Old Brompton Road, London SW7 3RP, UK. Tel. +44 2087224029.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

June 24, 2020

COVID-19–related Mortality During the First 60 Days After Kidney Transplantation

Julio Pascual [a,], Edoardo Melilli [b], Carlos Jiménez-Martín [c], Esther González-Monte [d], Sofía Zárraga [e], Alex Gutiérrez-Dalmau [f], Veronica López-Jiménez [g], Javier Juega [h], Miguel Muñoz-Cepeda [i], Inmaculada Lorenzo [j], Carme Facundo [k], María del Carmen Ruiz-Fuentes [l], Auxiliadora Mazuecos [m], Emilio Sánchez-Álvarez [n], Marta Crespo [a]*

The COVID-19 pandemic prompted the decision to suspend most organ transplantation programs in affected countries, especially in Europe [1]. A recent large population-based report revealed that the cohort at highest risk of in-hospital death due to COVID-19 was the organ transplant population, with a hazard ratio of 4.27 [2]. Published experiences

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Research Letter

Inferior Cancer Survival for Men with Localized High-grade Prostate Cancer but Low Prostate-specific Antigen

Christian D. Fankhauser[a,b,c,*], *Kathryn L. Penney*[b,d], *Amparo G. Gonzalez-Feliciano*[b], *Noel W. Clarke*[c], *Thomas Hermanns*[a], *Konrad H. Stopsack*[e], *Michelangelo Fiorentino*[f], *Massimo Loda*[g], *Brandon Mahal*[h,i], *Travis A. Gerke*[j], *Mark A. Preston*[k], *Lorelei A. Mucci*[b]

Results from the Surveillance, Epidemiology and End Results (SEER) Program and National Cancer Data Base (NCDB) indicate that among men with localized, high-grade prostate cancer, those with low prostate-specific antigen (PSA) levels at diagnosis have worse prognosis compared to men with intermediate PSA levels [1]. This prior analysis was based on data with rather short median follow-up of only 2–4 yr, which is limited given the long natural history of prostate cancer, and only reported on a limited number of prostate cancer deaths. The aim of our analysis was to validate these findings among men with Gleason score 8–10 prostate cancer within the US Health Professionals Follow-up Study (HPFS). Gleason scores were re-reviewed by experienced genitourinary pathologists according to the most recent grading recommendations [2]. The primary endpoint was lethal prostate cancer, defined as death from prostate cancer or the development of metastases during follow-up.

The association between PSA and lethal prostate cancer was modeled using restricted cubic splines with four knots and Cox regression.

Of 4908 men with localized prostate cancer diagnosed between 1988 and 2015 and data on PSA available at diagnosis and follow-up, 716 had Gleason score 8–10 tumors. The median age at diagnosis was 70 yr (interquartile range 66–77). Primary treatment included radical prostatectomy (43%), radiotherapy (33%), brachytherapy (8%), hormonal therapy (9%), and watchful waiting or other therapies (9%; Supplementary Table 1). Over median follow-up of 13 yr (interquartile range 8–19), 156 men (22%) experienced progression to lethal prostate cancer and 259 (36%) noncancer deaths occurred. The association between diagnostic PSA levels and lethal disease is presented in Fig. 1A. After adjustment for clinical stage, Gleason score, and treatment received, men with low PSA (<5 ng/mL) at diagnosis were at higher risk of lethal progression compared to men with intermediate PSA levels (5–8 ng/ml; hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.05–3.20). Men with high PSA (>8 ng/mL) also had an excess risk of lethal prostate cancer (HR 2.14, 95% CI 1.35–3.40) compared to those with intermediate PSA. Competing-risk analyses revealed that all-cause mortality exceeded lethal cancer events among the whole cohort and that lethal prostate cancer was more common for men with low or high PSA at diagnosis (Fig. 1B).

These results suggest a J-shaped rather than a linear association between PSA and lethal disease among men with localized high-grade prostate cancer. Data from this prospective cohort with long-term follow-up confirm prior findings of worse oncological outcomes for men with high-grade prostate cancer and low PSA at diagnosis. Previous research suggested that altered neuroendocrine/small-cell histology and androgen receptor signaling might be a reason for the inferior oncological outcomes [1]. This may explain why men with high-grade prostate cancer and low PSA often respond differently to primary or salvage therapies [3]. Our data support the need for an amended clinical definition of "highest-risk" localized prostate cancer expanded to include men in the low PSA group. Further research is needed to explore genomic and/or genetic tests,

https://doi.org/10.1016/j.eururo.2020.05.035

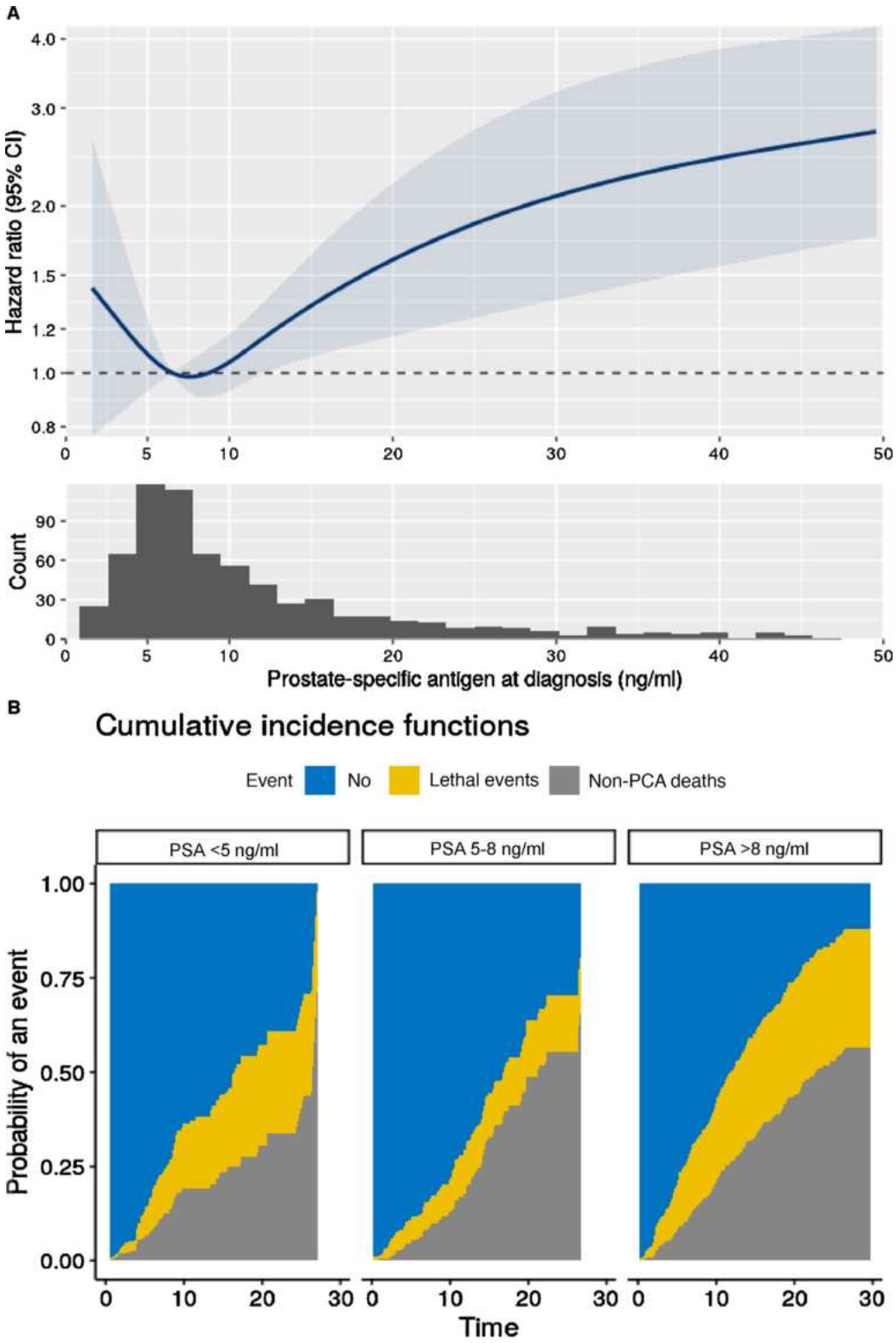


Fig. 1 – Lethal prostate cancer (PCA) according to prostate-specific antigen (PSA) levels at cancer diagnosis among men diagnosed with localized, Gleason score 8–10 PCA between 1986 and 2015 within the Health Professional Follow-up Study. (A) Multivariable hazard ratios from Cox proportional hazards regression, with PSA modeled as a restricted cubic spline, adjusted for clinical stage, Gleason score, and treatment received. The solid curve represents point estimates and the highlighted blue area the 95% confidence interval (CI). (B) Cumulative incidence of lethal PCA (yellow) and all-cause mortality (gray) among men with high or low PSA levels compared to men with intermediate PSA levels.

lifestyle modification, and different treatment regimens for this group.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: This study was supported by funding for C.D.F. from the University Hospital of Zurich and medAlumni Zurich, Stiftung für urologische Forschung, Marlis Geiser-Lemken Stiftung, Fonds zur Förderung des akademischen Nachwuchses, Ernst Göhner Stiftung, a SAKK/Dr. Paul Janssen Fellowship, and Arnold U. und Susanne Huggenberger-Bischoff Stiftung zur Krebsforschung; and for L.A.M. from the National Institutes of Health (U01 CA167552), the US Army Prostate Cancer Research Program (Idea Development Award PC060389, an Early-Investigator Research Award (W81XWH-18-1-0330), and Dana-Farber/Harvard Cancer Center Prostate SPORE Career Development Award (NIH/NCI P50 CA090381). L.A.M., K.L.P., K.H.S., and M.A.P. are Young Investigators of the Prostate Cancer Foundation. The funding bodies had no influence on the design or conduct of the study, analysis and interpretation of the data, or preparation of the article. We are grateful to the participants and staff of the Health Professionals Follow-up Study for their valuable contributions. We also thank the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nevada, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.05.035.

References

[1] Mahal BA, Yang DD, Wang NQ, et al. Clinical and genomic characterization of low–prostate-specific antigen, high-grade prostate cancer. Eur Urol 2018;74:146–54.
[2] Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? J Clin Oncol 2009;27:3459–64.
[3] Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. Nat Med 2017;23:664.

[a]*Department of Urology, University Hospital Zurich, University of Zurich, Zurich, Switzerland*
[b]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[c]*Department of Urology, The Christie and Salford Royal NHS Foundation Trusts, Manchester, UK*
[d]*Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[e]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[f]*Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna School of Medicine, Bologna, Italy*
[g]*Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA*
[h]*Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[i]*McGraw/Patterson Center for Population Sciences, Boston, MA, USA*
[j]*Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, USA*
[k]*Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

*Corresponding author. Department of Urology, University Hospital of Zurich, University of Zurich, Frauenklinikstrasse 10, Zurich 8091, Switzerland. Tel. +41 44 2551111.
E-mail address: christian.fankhauser@usz.chf (C.D. Fankhauser).

Elucidating Durable Responses to Immune Checkpoint Inhibition

Pasquale Rescigno [a,b], Caterina Aversa [a], Mateus Crespo [a], George Seed [a], Maryou Lambros [a], Bora Gurel [a], Ines Figueiredo [a], Diletta Bianchini [b], Ruth Riisnaes [a], Rita Pereira [a], Maria D. Fenor de la Maza [a,b], Juliet Carmichael [a,b], Khobe Chandran [b], Ana Ferreira [a], Claudia Bertan [a], Alec Paschalis [a,b], Andra Curcean [b], Adam Sharp [a,b], Wei Yuan [a], Nina Tunariu [a,b], Christian Poehlein [c], Suzanne Carreira [a], Johann S. de Bono [a,b,]*

Immune checkpoint inhibitors (ICIs) are under investigation for metastatic castration-resistant prostate cancer (mCRPC) [1]. Mismatch DNA repair deficiency (MMRd) [2] and high tumour lymphocyte infiltration (TIL) [3] represent biomarkers of ICI response. Here we report on two mCRPC patients with exceptional responses to pembrolizumab, outlining their disease biology in attempts to explain this sensitivity (previous oncological history is reported in the Supplementary material).

In November 2016, patient 1 started pembrolizumab 200 mg every 3 wk, when his baseline prostate-specific antigen (PSA) was 59 μg/l and scans showed a right external iliac nodal mass (Fig. 1A). The main adverse events were grade 4 hyperamylasaemia and grade 2 sicca syndrome, requiring a treatment break and high-dose steroids. He experienced a complete radiological response, with undetectable PSA, which persists 40 mo after starting pembrolizumab (Fig. 1B,C). Immunohistochemistry (IHC) studies were positive for

Patient 2 commenced pembrolizumab 200 mg every 3 wk in November 2016; his PSA was 0.43 μg/l and scans revealed bilateral pelvic nodes, a large pelvic mass (53 mm), and a complex fistula between the rectum and bladder. He received 11 pembrolizumab courses with no immunological toxicity and experienced a partial response. However, pembrolizumab was stopped because of fistula worsening requiring intravenous antibiotics and surgical intervention. He made a full recovery and remains disease-free 40 mo after starting pembrolizumab (Fig. 1F,G). Tumour NGS had indicated an MSH6 mutation (Y214*), high MutLoad, and high MSINGS score, with MSH6 loss but incomplete MSH2 loss on IHC, as well as PD-L1 positivity (1%). IHC showed high TILs; most of these cells were $CD4^+$FOXP3 and Tregs ($CD4^+FOXP3^+$; Fig. 1H).

We previously showed that a small but important subset of mCRPC tumours have evidence of MMRd by IHC and this is associated with high MutLoad and MSI-NGS. However, only some MMRd cancers present with high T-cell infiltration, PD-L1 protein expression, and elevated T-cell–associated transcripts [2].

The rearrangement identified for patient 1 was associated with immune evasion and PD-L1 overexpression in mouse models using an N-terminal binding antibody [4]. This could explain his PD-L1 negativity (since the antibodies routinely used target the C-terminus) and extraordinary response to pembrolizumab in an otherwise immune "cold" tumour.

Patient 2, besides MMRd, presented with a highly inflamed cancer, mainly represented by Tregs and $CD4^+$FOXP3 cells. Interestingly, in mCRPC models, ICIs reprogram $CD4^+$ cells towards a Th1 rather than Th17 lineage in nodal disease, possibly explaining this responsiveness [5].

In conclusion, elucidation of the mCRPC subset benefiting from ICIs requires multiple orthogonal assays, including genomic analyses, IHC, and tumour microenvironment studies.

Conflicts of interest: Johann S. de Bono has served on advisory boards for MSD, Merck Serono, Pfizer, Genentech/Roche, AstraZeneca, Astellas, Janssen, GSK, Genmab, Amgen, Daiichi Sankyo, and Bayer. The remaining authors have nothing to disclose.

Acknowledgements: Christian Poehlein is an employee of Merck Sharp&Dohme. Pasquale Rescigno is supported by a Prostate Cancer Foundation (PCF) Young Investigator Award.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.056.

References

[1] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395–405.

[2] Rodrigues DN, Rescigno P, Liu D, et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest 2018;128:4441–53.

[3] Daud AI, Loo K, Pauli ML, et al. Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma. J Clin Invest 2016;126:3447–52.

[4] Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. Nature 2016;534:402–6.

[5] Jiao S, Subudhi SK, Aparicio A, et al. Differences in tumor microenvironment dictate T helper lineage polarization and response to immune checkpoint therapy. Cell 2019;179, 1177–90.e13.

[a]*The Institute of Cancer Research, London, UK*
[b]*The Royal Marsden Hospital, London, UK*
[c]*Merck & Co., Kenilworth, NJ, USA*

*Corresponding author. The Institute of Cancer Research, 123 Old Brompton Road, London SW7 3RP, UK. Tel. +44 2087224029.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

June 24, 2020

COVID-19–related Mortality During the First 60 Days After Kidney Transplantation

Julio Pascual [a,], Edoardo Melilli [b], Carlos Jiménez-Martín [c], Esther González-Monte [d], Sofía Zárraga [e], Alex Gutiérrez-Dalmau [f], Veronica López-Jiménez [g], Javier Juega [h], Miguel Muñoz-Cepeda [i], Inmaculada Lorenzo [j], Carme Facundo [k], María del Carmen Ruiz-Fuentes [l], Auxiliadora Mazuecos [m], Emilio Sánchez-Álvarez [n], Marta Crespo [a]*

The COVID-19 pandemic prompted the decision to suspend most organ transplantation programs in affected countries, especially in Europe [1]. A recent large population-based report revealed that the cohort at highest risk of in-hospital death due to COVID-19 was the organ transplant population, with a hazard ratio of 4.27 [2]. Published experiences

Table 1 – Characteristics of 24 patients who suffered from COVID-19 during the first 60 d after kidney transplantation.

Variable	Alive (n = 13)	Dead (n = 11)	p value
Male, n (%)	6 (46.2)	5 (45.5)	0.97
Median age, yr (range)	61.1 (40–74)	69.6 (60–75)	0.006
Age ≥65 yr, n (%)	4 (30.8)	8 (72.7)	0.04
Hypertension, n (%)	12 (92.3)	10 (90.9)	1
Diabetes, n (%)	8 (66,7)	4 (36.4)	0.15
Deceased donor, n (%)	13 (100)	10 (91)	0,46
Delayed graft function n (%)	5 (38.5)	7 (63.6)	0.41
Acute rejection, n (%)	2 (15.4)	0 (0)	0.48
Median time from KT to COVID-19 Dx, d (range)	39 (15–59)	28.8 (8–56)	0.07
Baseline immunosuppressive treatment, n (%)			
Prednisone	13 (100)	11 (100)	1
Tacrolimus	13 (100)	11 (100)	1
Mycophenolate	12 (92,3)	9 (81.8)	0.58
mTOR inhibitors	0 (0)	2 (18.2)	0.2
Fever, n (%)	9 (69.2)	6 (54.5)	0.67
Cough, expectoration, and/or rhinorrhea, n (%)	6 (46.2)	8 (72.7)	0.24
Dyspnea, n (%)	6 (46.2)	8 (72.7)	0.24
Pneumonia, n (%)	12 (92.3)	10 (90.9)	1
Digestive symptoms, n (%)	1 (7.7)	2 (18.2)	0.58
Lymphopenia, n (%)	13 (100)	11 (100)	1
Hospitalization, n (%)	13 (100)	11 (100)	1
Renal failure, n (%)	6 (46.2)	7 (63.6)	0.26
Ventilator support, n (%)	2 (15.4)	7 (77.8)	0.007
Intensive care unit admission, n (%)	2 (15.4)	2 (18.2)	1
COVID-19 treatment, n (%)			
Hydroxychloroquine	12 (92.3)	10 (90.9)	1
Glucocorticoids	3 (25)	9 (81.8)	0.006
Lopinavir/ritonavir	4 (30.8)	4 (36.4)	1
Tocilizumab	5 (38.5)	3 (27.3)	0.68
Median time from admission to death or recovery, d (range)	23 (4–48)	13.7 (6–36)	0.08

KT = kidney transplantation; Dx = diagnosis.

have been restricted to long-term stable kidney transplant (KT) recipients. Despite initial low mortality reported from China [3], further case series have shown mortality rates of up to 75% [4]. The decision to suspend KT programs has been arbitrary, as no reports of COVID-19 in the most vulnerable population, that is, patients with a very recent KT and profound immunosuppression, are available.

A registry to collect information regarding dialysis or KT patients with COVID-19 in Spain started to gather information on March 18, 2020 (www.senefro.com). A confirmed COVID-19 diagnosis was defined as a patient with positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a specimen collected via nasopharyngeal swab or bronchoalveolar lavage. Comparisons between groups were made using a two-sided χ^2 test with a significance level of 0.05, using SPSS v22. The study was approved by the ethics committee of Hospital del Mar.

Among the 502 KT patients with COVID-19 included until May 9, 2020, 24 had received a KT less than 60 d before being diagnosed as having COVID-19. Cases were diagnosed in 12 Spanish transplant centers between March 17 and April 18, 2020 and had at least 1 mo of follow-up. During the period and 60 d before the first case, 275 KT surgeries were performed in those 12 centers. Therefore, the cumulative incidence of COVID-19 was 9%.

The median age of the 24 patients was 66.5 yr (range 40–75) and immunosuppression regimens were conventional (Table 1). Fever, cough, and pneumonia were the usual COVID-19 signs and symptoms and all of the patients were hospitalized. Respiratory failure led to ventilatory support in eight patients and intensive care unit (ICU) admission in four. ICU admission was initially indicated but finally denied in nine patients. Specific COVID-19 management was attempted with immunosuppression reduction (mycophenolate withdrawal in 96% and tacrolimus withdrawal in 62.5%) and different combinations of hydroxychloroquine, antiviral agents, and steroids. Interestingly, eight patients were treated with the anti-IL6 antibody tocilizumab and five of them recovered. No relevant surgical or urological complications were recorded.

The fatality rate was 45.8%, which is markedly higher than the usual very low 2-mo mortality observed outside the COVID-19 pandemic. Compared with survivors, patients who died were older, were infected closer to transplantation, more frequently needed ventilator support, and were treated less often with high-dose steroids.

The maximum effect of immunosuppression is exerted in the first months after transplantation and recipients are at maximum risk of viral infection and severity in this period. A short time since transplantation was associated with more severe disease in the 2009 pandemic of influenza A (H1N1) [5]. In cities and areas with very high incidence of COVID-19, KT is not a safe option for renal patients, especially those aged >60 yr. When COVID-19 significantly decreases, and as part of

the measures to open up after lockdown, KT programs may be resumed under strict preventive measures.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: We are indebted to the many physicians and nurses who take care of these patients and are facing the COVID-19 pandemic in our country. The registry for COVID-19 renal patients is supported by the Spanish Society of Nephrology.

CRediT authorship contribution statement

Julio Pascual: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft. **Edoardo Melilli:** Investigation, Writing - review & editing. **Carlos Jiménez-Martín:** Investigation, Writing - review & editing. **Esther González-Monte:** Investigation, Writing - review & editing. **Sofía Zárraga:** Investigation, Writing - review & editing. **Alex Gutiérrez-Dalmau:** Investigation, Writing - review & editing. **Veronica López-Jiménez:** Investigation, Writing - review & editing. **Javier Juega:** Investigation, Writing - review & editing. **Miguel Muñoz-Cepeda:** Investigation, Writing - review & editing. **Inmaculada Lorenzo:** Investigation, Writing - review & editing. **Carme Facundo:** Investigation, Writing - review & editing. **María del Carmen Ruiz-Fuentes:** Investigation, Writing - review & editing. **Auxiliadora Mazuecos:** Investigation, Writing - review & editing. **Emilio Sánchez-Álvarez:** Investigation, Writing - review & editing. **Marta Crespo:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft.

References

[1] Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet 2020;395:e95–6. http://dx.doi.org/10.1016/S0140-6736(20)31040-0.

[2] The OpenSAFELY Collaborative. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv preprint. https://doi.org/10.1101/2020.05.06.20092999.

[3] Zhang H, Chen Y, Yuan Q, et al. Identification of kidney transplant recipients with coronavirus disease 2019. Eur Urol 2020;77:742–7. http://dx.doi.org/10.1016/j.eururo.2020.03.030.

[4] Abrishami A, Samavat S, Behnam B, Arab-Ahmadi M, Nafar M, Sanei Taheri M. Clinical course, imaging features, and outcomes of COVID-19 in kidney transplant recipients. Eur Urol 2020;78:281–6. http://dx.doi.org/10.1016/j.eururo.2020.04.064.

[5] Cordero E, Pérez-Romero P, Moreno A, et al. Pandemic influenza A (H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection. Clin Microbiol Infect 2012;18:67–73. http://dx.doi.org/10.1111/j.1469-0691.2011.03537.x.

[a]*Department of Nephrology, Hospital del Mar, Barcelona, Spain*
[b]*Department of Nephrology, Hospital Universitari Bellvitge, Hospitalet del Llobregat, Barcelona, Spain*
[c]*Department of Nephrology, Hospital Universitari La Paz, Madrid, Spain*
[d]*Department of Nephrology, Hospital Universitari 12 Octubre, Madrid, Spain*
[e]*Department of Nephrology, Hospital de Cruces, Bilbao, Spain*
[f]*Department of Nephrology, Hospital Miguel Servet, Zaragoza, Spain*
[g]*Department of Nephrology, Hospital Universitari Carlos Haya, Málaga, Spain*
[h]*Department of Nephrology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*
[i]*Department of Nephrology, Hospital Virgen de la Salud, Toledo, Spain*
[j]*Department of Nephrology, Hospital General de Albacete, Spain*
[k]*Department of Nephrology, Fundació Puigvert, Barcelona, Spain*
[l]*Department of Nephrology, Hospital Virgen De Las Nieves, Granada, Spain*
[m]*Department of Nephrology, Hospital Puerta del Mar, Cádiz, Spain*
[n]*Department of Nephrology, Hospital de Cabueñes, Gijón, Spain*
*Corresponding author. Department of Nephrology, Hospital del Mar, Passeig Maritim 25-29, 08003 Barcelona, Spain. Tel. +34 66 6478630.

June 12, 2020

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Lan Zhu, Nianqiao Gong, Bin Liu, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. Eur Urol 2020;77:748–54

We read with great interest the case series by Zhu et al [1]. We applaud their commitment to their patients in these difficult times. However, we feel that some questions remain unanswered. Did the authors check for the presence of bacterial and/ or fungal co-infection in sputum, as has been commonly seen in patients with COVID-19infection [2]? Such co-infections may have contributed to the respiratory symptoms, especially in case of the transplant patients. Tian et al [3] recently reported on the presence of superimposed bacterial bronchopneumonia in post-mortem lung biopsy specimens from COVID-19 patient.

The authors should also report the criteria for starting and stopping IVIG, since we noticed that patient number 7, who had mild disease, received IVIG, but patients 3 and 8, who had critical disease, did not receive IVIG. We noted that patients 2 and 9 had several comorbidities and experienced a severe clinical course. Yang et al [2] recently reported a severe clinical course and higher mortality among non-transplant patients with comorbidities such as cardiovascular disease and diabetes mellitus, so how can the authors be sure that the severe course of COVID-19 in their transplant patients was entirely due to immunosuppression, especially as we have no data regarding comorbidities in the control group for comparison? Diabetic nephropathy is the second leading cause of end-stage renal disease in China after primary glomerulonephritis [4], so it is surprising to see that none of the patients in the current series were diabetic. We would urge the authors to check the diabetic status of their patients, as diabetes was noted among 22% of the patients who died in one study, versus 10% among the survivors [2].

We feel that answers to the above-mentioned queries will help us to better understand the clinical course of COVID-19 infection in renal transplant patients. This type of study on a larger scale with the above-mentioned questions answered might help us to better understand the contribution of comorbidities and immunosuppression individually towards the severity of this disease.

We would like to conclude by thanking the authors for sharing their knowledge and contributing towards the collective scientific effort and knowledge.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Zhu L, Gong N, Liu B, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan. China Eur Urol 2020;77:748–54. http://dx.doi.org/10.1016/j.eururo.2020.03.039.

[2] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81. http://dx.doi.org/10.1016/S2213-2600(20)30079-5.

[3] Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Modern Pathology 2020;33(6):1007–14, Jun 1.

[4] Xie Y, Chen X. Epidemiology, major outcomes, risk factors, prevention and management of chronic kidney disease in China. Am J Nephrol 2008;28:1–7. http://dx.doi.org/10.1159/000108755.

Amit Bansal*
Anant Kumar
Department of Urology, Robotics and Renal Transplant, Max Super Speciality Hospital Saket, New Delhi, India

*Corresponding author. Department of Urology, Robotics and Renal Transplant, Max Super Speciality Hospital Saket, 1–2 Press Enclave Marg, Saket, New Delhi 110017, India. Tel. +91 9501969524.
E-mail address: dramitbansalurology@gmail.com (A. Bansal).

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.062.
https://doi.org/10.1016/j.eururo.2020.06.058

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Reply to Amit Bansal and Anant Kumar's Letter to the Editor re: Lan Zhu, Nianqiao Gong, Bin Liu, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. Eur Urol 2020;77:748–54

We thank Drs. Bansal and Kumar for their questions and interest in our paper [1]. Owing to the word limit, some information was not provided in detail in our paper. Here we answer their questions and provide supplementary explanations.

We agree that a combination of bacterial or fungal infections during COVID-19 could aggravate a patient's condition and lead to a poor prognosis. Because some of our patients had almost no sputum during the whole course of the disease, a sputum culture was not carried out for all ten of our patients. However, the clinical course and the sputum culture results obtained for some of the patients indicated that there was no evidence of bacterial or fungal co-infection.

The absence of co-infection was probably related to our prophylactic strategy: all patients were routinely given broad-spectrum antibiotics (eg, carbapenem or sulbactam/cefoperazone) after admission, and patients with a longer course of illness were given echinocandins to prevent fungal infections [2]. Although Yang et al [3] reported 13.5% incidence of hospital-acquired bacterial or fungal co-infection, all of the patients they observed were critically ill patients requiring treatment in the intensive care unit (ICU), and nearly half received invasive ventilation. By contrast, only one of the ten patients in our study required short-term treatment in the ICU, and none received invasive ventilation. This difference in incidence of critical illness may also be an important reason for the difference in the incidence of co-infection between the two studies. Regarding the use of intravenous immunoglobulin (IVIG), we recommend that transplant recipients with COVID-19 should receive a small daily dose of IVIG during the early period of their hospitalization, until chest computed tomography shows a significant improvement in inflammation. However, since our ten patients were admitted to five different designated hospitals, three of the patients did not receive IVIG because of the lack of that resource in the corresponding hospital at the time.

We agree that underlying diseases are associated with the severity, duration, and prognosis of COVID-19 pneumonia in some patients. We should have emphasized the impact of comorbidities more strongly in our paper. Three of our patients had severe and complex underlying diseases, which contributed to the death of one patient and to severe illness that required treatment in the ICU in another patient. However, the remaining patients without underlying disease (four cases) or with controllable hypertension alone (three cases) still had more severe COVID-19 pneumonia and a longer viral shedding time than the control group did, indicating that immunosuppressive status is the most important factor affecting the clinical progression of COVID-19 in most transplant patients. Although diabetic nephropathy is a common cause of end-stage renal failure, such patients receive simultaneous pancreas-kidney transplantation rather than simple kidney transplantation in China [4,5]. In our study, none of the ten renal transplant patients had primary diabetic nephropathy or new-onset diabetes mellitus after transplantation. Only one individual (patient 2) experienced transient hyperglycemia during treatment of pneumonia, but the patient's blood glucose returned to normal shortly after reduction of glucocorticoid treatment.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Zhu L, Gong N, Liu B, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan. China Eur Urol 2020;77:748–54. http://dx.doi.org/10.1016/j.eururo.2020.03.039.

[2] Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020;20:1859–63.

[3] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.

[4] Ming C, Gong N, Chen X. The current state of pancreas-kidney transplantation in China: the indications, surgical techniques and outcome. J Huazhong Univ Sci Technol Med Sci 2009;29:269–72.

https://doi.org/10.1016/j.eururo.2020.06.062

[5] Zhang L, Chen Z, Lai X, et al. The homolateral simultaneous pancreas-kidney transplantation: a single-center experience in China. Ann Transl Med 2019;7:629.

Lan Zhu[a,b]
Gang Chen[a,b,*]

[a]*Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

[b]*Key Laboratory of Organ Transplantation, Ministry of Education, Ministry of Public Health, Chinese Academy of Medical Sciences, Wuhan, China*

[*]Corresponding author. Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Tel. +86 27 83662892; Fax: +86 27 83662892.
E-mail address: gchen@tjh.tjmu.edu.cn (G. Chen).

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Marc-Oliver Grimm, Antione G. van der Heijden, Marc Colombel, et al. Non–muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.066

We read with great interest the article by Grimm et al [1] on the study of 170 patients randomized to a reduced frequency and 175 to the standard bacillus Calmette-Guérin (BCG) schedule. The authors demonstrated that the reduced frequency schedule was inferior to the standard schedule for treatment of high-grade non–muscle-invasive bladder carcinoma (NMIBC) regarding the time to first recurrence. However, we would like to highlight some issues.

First, the authors reported that the randomization stratification of the study included Ta versus T1, concomitant carcinoma in situ (CIS) versus no CIS, BCG strain, and single versus multiple tumors. However, it has been demonstrated that age, gender, tumor size, and prior recurrence rate are also related to recurrence among patients treated with BCG [2,3]. Although the proportion of patients with recurrent tumors and gender distributions are similar in the study arms, information on tumor size and the age of participants are not reported. The multivariate Cox regression model of the CUETO study showed that age increases the risk of recurrence (hazard ratio [HR] 1.168, 95% confidence interval [CI] 1.015–1.343 for age groups of $<$60 vs 60–70 vs $>$70 yr; $p = 0.03$) [3]. In addition, Sylvester et al [2] reported that tumor size and multiplicity increased the recurrence rate among patients treated with intravesical BCG instillations (HR 1.54, 95% CI 1.32–1.80 for tumor size of $\leq$3 vs $\geq$3 cm, $p <$ 0.0001; HR 1.56, 95% CI 1.42–1.71 for tumor multiplicity of 1 vs 2–7 vs $\geq$8, $p <$ 0.0001). We believe that tumor size, patient age, and tumor multiplicity may affect the results of this study and are worthy of discussion.

It is of note that the recurrence rate in the standard BCG frequency arm of the study was 8% at 6 mo and 10% at 12 mo, which seems to be fairly low in comparison to results from previous studies [3,4]. Cambier et al [4] observed a recurrence rate of 17.5% in their study, in which they described early recurrence as 4.5 mo after randomization. For the 2-yr recurrence rate in the standard treatment arm, the results in the present study are similar to the lowest scored patient group in the CUETO study (14% vs 12.6%) [3]. These details suggest that results from the study arms in this trial may not be appropriate to guide daily practice.

In conclusion, we believe that intravesical BCG therapy for the treatment of intermediate- and high-risk NMIBC is still an issue for further discussion and research. We congratulate the authors of this multi-institutional study on this recent report, which clearly contributes in our fight against NMIBC.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Grimm M.-O.-O, van der Heijden A.G., Colombel M., et al. Treatment of high-grade non–muscle-invasive bladder carcinoma by standard number and dose of BCG instillations versus reduced number and standard dose of BCG instillations: results of the European Association of Urology Research Foundation randomised phase III clinical trial "NIMBUS". Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.066.

[2] Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–77.

[3] Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting non-muscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009;182:2195–203.

[4] Cambier S, Sylvester RJ, Collette L, et al. EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1-3 years of maintenance bacillus Calmette-Guerin. Eur Urol 2016;69:60–9.

DOI of original article: https://doi.org/10.1016/j.eururo.2020.07.004.

https://doi.org/10.1016/j.eururo.2020.06.060

Emre Karabay[a,*]
İlker Tınay[b]

[a]*Department of Urology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey*
[b]*Department of Urology, Marmara University School of Medicine, Istanbul, Turkey*

*Corresponding author. Department of Urology, University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Tıbbıye Cad. 23, Uskudar, Istanbul 34668, Turkey. Tel. +90 2165423232.
E-mail address: emrekarabay@gmail.com (E. Karabay).

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Reply to Emre Karabay and İlker Tınay's Letter to the Editor re: Treatment of High-grade Non–muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.066

We thank the authors for their useful comments and reflections addressing our publication [1]. We agree that age, gender, prior recurrence rate, multiplicity, and tumor size might influence the outcome after bacillus Calmette-Guérin (BCG) for high-grade non–muscle-invasive bladder cancer (NMIBC). Tumor size was, regrettably, not sufficiently recorded in NIMBUS. Multiplicity was a stratification factor and, like the other criteria mentioned, well balanced between the NIMBUS study arms. Median patient age, not mentioned in the NIMBUS publication, was 70 yr in both arms (range 39–86 vs 35–86 yr).

Two of the most important findings from NIMBUS apart from the intended outcome measures were the very low recurrence and progression rates (R&PRs) in the standard treatment arm as compared to the CUETO and EORTC risk tables [2,3]. However, age and gender only contribute to the CUETO and not the EORTC risk scores. It has already been reported that the EORTC risk calculator overestimates R&PRs [4]. In an additional analysis, we therefore scored each NIMBUS patient in the BCG standard arm according to CUETO criteria [2] and compared the estimated recurrence rates (RRs) with the corresponding CUETO probabilities (Table 1).

The 1-yr and 2-yr RRs appear slightly higher for low-risk patients (scores 0–4) compared to the CUETO data. However, in NIMBUS only a few events occurred and the confidence intervals are wide. For patients with intermediate and high risk (score 5–6 and 7–9), the 1-yr and 2-yr RRs are similar and clearly lower when compared with the CUETO tables. In the highest risk category (score $\geq$10) there were too few patients to calculate reliable values. Compared to CUETO, applying the EORTC risk estimates to the NIMBUS population indicated even higher RRs, although tumor size was not taken into account.

Very few individuals in the NIMBUS population experienced progression at their first recurrence, suggesting lower progression rates than expected from the CUETO tables, but hindering us from generating a reliable comparison. The final analysis of NIMBUS will provide more mature progression data.

In summary, low R&PRs in NIMBUS cannot be explained by different risk factors in the study population. In contrast to our patients, the EORTC population most frequently received intravesical chemotherapy and a minority received BCG induction only [3], whereas the CUETO population received six BCG induction cycles, followed by six additional biweekly instillations. Unlike in NIMBUS, repeat transurethral resection (TUR) was not mandatory in the CUETO and EORTC studies at that time [2]. Besides a possible impact of technical improvements, such as the use of improved video systems or photodynamic diagnostics, we attribute the low R&PRs in NIMBUS to the routine repeat TUR before BCG induction (92% of patients). Such re-intervention might be of diagnostic and therapeutic value. Patients are better classified, possibly leading to other

Table 1 – Recurrence rates by CUETO risk category after 1 and 2 yr among 175 patients.

CUETO Score	Patients, *n* (%)	1-yr result (95% CI)		2-yr result (95% CI)	
		Recurrence, %	CUETO PoR	Recurrence, %	CUETO PoR
Score 0–4	47 (26.9)	18 (6.0–31)	8.2 (5.9–11)	22 (8.3–37)	13 (9.8–15)
Score 5–6	65 (37.1)	9.8 (1.6–18)	12 (8.0–16)	17 (4.8–30)	22 (17–28)
Score 7–9	47 (26.9)	5.3 (1.8 to 12)	25 (20–31)	5.3 (1.8 to 12)	40 (33–46)

PoR = probability of recurrence; CI = confidence interval.

DOI of original article: https://doi.org/10.1016/j.eururo.2020.06.060.

https://doi.org/10.1016/j.eururo.2020.07.004

treatments such as cystectomy in some. This may play a major role, specifically in the higher risk categories. Furthermore, complete tumor removal may improve RRs [5].

In conclusion, considering established risk factors, NIMBUS supports that standard BCG therapy after complete tumor resection results in low R&PRs in high-grade NMIBC and remains the state of the art. If long-term results confirm our findings, the risk estimates from current risk calculators should be reconsidered.

Conflicts of interest: Marc Oliver Grimm reports grants and personal fees from Novartis and BMS; and personal fees from Pfizer, Bayer HealthCare, Astellas, Intuitive Surgical, Sanofi Aventis, Hexal, Apogepha, Amgen, AstraZeneca, MSD, Janssen Cilag, Ono Pharma, Ipsen Pharma, Medac, and Merck, outside the submitted work. Christien Caris and Wim P.J. Witjes have nothing to disclose.

Acknowledgements: We thank all patients and their families, as well as all NIMBUS investigators. Funding: Deutsche Krebshilfe (DKH 109724); MEDAC (provision of BCG Medac in reduced frequency arm in Germany); Hospital Edouard Herriot, Department of Urology, Lyon, France; Jena University Hospital, Department of Urology, Jena, Germany; EAU research foundation.

References

[1] Grimm MO, van der Heijden AG, Colombel M, et al. Treatment of high-grade non-muscle-invasive bladder carcinoma by standard number and dose of BCG instillations versus reduced number and standard dose of BCG instillations: results of the European Association of Urology Research Foundation randomised phase III clinical trial "NIMBUS". Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.04.066.

[2] Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting non-muscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009;182:2195–203.

[3] Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:Error: FPage (466) is higher than LPage (477)!.

[4] Fernandez-Gomez J, Madero R, Solsona E, et al. The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: external validation of the EORTC risk tables. Eur Urol 2011;60:423–30.

[5] Sfakianos JP, Kim PH, Hakimi AA, Herr HW. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guerin. J Urol 2014;191:341–5.

Marc-Oliver Grimm[a,*]
Christien Caris[b]
Wim P.J. Witjes[b]
for the NIMBUS study group

*Corresponding author. Department of Urology University Hospital of Jena, Am Klinikum 1, 07747, Jena, Germany Tel: +49 3641 9329901 Fax: +49 3641 9329902.
E-mail address: marc-oliver.grimm@med.uni-jena.de (M.-O. Grimm).
[a]*Department of Urology, University Hospital of Jena, Jena, Germany*

[b]*EAU Research Foundation, Arnhem, The Netherlands*

July 2, 2020

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Vasilis Stavrinides, Francesco Giganti, Bruce Trock, et al. Five-year Outcomes of Magnetic Resonance Imaging–based Active Surveillance for Prostate Cancer: A Large Cohort Study. Eur Urol 2020;78:443–51

We read with interest the recent article by Stavrinides et al [1] reporting on 5-yr outcomes of magnetic resonance imaging (MRI)–based active surveillance for prostate cancer (PCa). While we agree with the authors' conclusion regarding the value of multiparametric MRI in the long-term assessment of PCa patients treated with active surveillance, we respectfully suggest that the contemporary clinical scenario has changed quite significantly. According to the latest version of the European Association of Urology prostate cancer guidelines, all patients with a clinical suspicion of PCa should initially be assessed with multiparametric MRI, and only patients for whom lesions with a Prostate Imaging-Reporting and Data System score of 4 or 5 are detected should undergo both fusion and systematic biopsies [2–4]. This means that at present and in an ideal world we should inevitably only be considering active surveillance for patients with one or more visible lesions on multiparametric MRI. Whether this new clinical scenario will lead to different long-term active surveillance results remains to be established.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging–based active surveillance for prostate cancer: a large cohort study. Eur Urol 2020;78:443–51.
[2] Mottet N, Cornford P, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer 2020. European Association of UrologyArnhem, The Netherlands https://uroweb.org/guideline/prostate-cancer/ 2020
[3] Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917–28.
[4] Venderink W, Bomers JG, Overduin CG, et al. Multiparametric magnetic resonance imaging for the detection of clinically significant prostate cancer: what urologists need to know. Part 3: targeted biopsy. Eur Urol 2020;77:481–90.

Francesco Montorsi*
Giorgio Gandaglia
Nicola Fossati
Andrea Salonia
Alberto Briganti
Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy

*Corresponding author. Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 02 26437286; Fax: +39 02 26437298.
E-mail address: montorsi.francesco@hsr.it (F. Montorsi).

July 7, 2020

DOI of original article: https://doi.org/10.1016/j.eururo.2020.07.010.
https://doi.org/10.1016/j.eururo.2020.07.008

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Reply to Francesco Montorsi, Giorgio Gandaglia, Nicola Fossati, Andrea Salonia, and Alberto Briganti's Letter to the Editor re: Vasilis Stavrinides, Francesco Giganti, Bruce Trock, et al. Five-year Outcomes of Magnetic Resonance Imaging–based Active Surveillance for Prostate Cancer: A Large Cohort Study. Eur Urol 2020;78:443–51

We thank the authors for their comments on our paper [1]. We agree that in the new world of magnetic resonance imaging before first biopsy for all men, we would hope that surveillance of non-visible prostate cancer will reduce, as these men would avoid the burden of diagnosis entirely. However, as many centres adopt a systematic biopsy approach in addition to targeted cores, we do see men with non-visible Gleason 3 + 3 and 3 + 4 disease, which we recognise could be of lower risk than visible disease. Given that some centres still offer these men radical prostatectomy and patients are often concerned by any diagnosis of prostate cancer, we think that active surveillance is an appropriate alternative response.

Using a risk-stratified active surveillance programme such as the one we outlined helps reduce the burden of surveillance for the individual man and healthcare systems in general.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: Vasilis Stavrinides is supported by an MRC Clinical Research Training Fellowship (MR/S005897/1) and the Mason Medical Research Foundation (PN: 558866) and acknowledges support from The Alan Turing Institute under EPSRC grant EP/N510129/1, as well as previous support from EACR (EACR Travel Fellowship) and UCL (Bogue Fellowship). Francesco Giganti is funded by the UCL Graduate Research Scholarship and the Brahm PhD scholarship in memory of Chris Adams. Mark Emberton receives research support from the UK National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2013. Caroline M. Moore acknowledges funding from the NIHR, the MRC, CRUK, Movember, PCUK, and the EAU Research Foundation.

Reference

[1] Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging–based active surveillance for prostate cancer: a large cohort study. Eur Urol 2020;78:443–51.

Vasilis Stavrinides[a,b,c,*]
Francesco Giganti[a,d]
Mark Emberton[a,b]
Caroline M. Moore[a,b]

[a]*Division of Surgery and Interventional Science, University College London, London, UK*
[b]*Department of Urology, University College London Hospital NHS Foundation Trust, London, UK*
[c]*The Alan Turing Institute, London, UK*
[d]*Department of Radiology, University College London Hospital NHS Foundation Trust, London, UK*

*Corresponding author. Division of Surgery and Interventional Science, University College London, Charles Bell House, 43–45 Foley Street, London W1T 7TS, UK.
E-mail address: v.stavrinides@ucl.ac.uk (V. Stavrinides).

July 7, 2020

DOI of original article: https://doi.org/10.1016/j.eururo.2020.07.008.
https://doi.org/10.1016/j.eururo.2020.07.010

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Reply to Guglielmo Mantica, Nazareno Suardi, and Carlo Terrone's Letter to the Editor re: Ming-Chun Chan, Sharon E.K. Yeo, Yew-Lam Chong, Yee-Mun Lee. Stepping Forward: Urologists' Efforts During the COVID-19 Outbreak in Singapore. Eur Urol 2020;78:e38–9

The insightful letter from Mantica et al in response to our article [1] reports a trend for a decrease in emergency department (ED) urological consultations in Italy during the COVID-19 lockdown and highlights two major issues for urologists. First, postponement of urological consultations carries a risk of potential rebound attendances in worsened condition and larger numbers. Our hospital implemented measures in anticipation of this, reviewing and triaging [2,3] all scheduled appointments and adopting telemedicine strategies including phone consultations and prescriptions (with courier delivery), a huge endeavour given the sheer volume of ambulatory patients. Second, the pandemic-related decrease in ED consultations is a reminder of the delicate balance in managing urological conditions in the community and tertiary settings.

Singapore and it's Ministry of Health implemented nation-wide "circuit breaker" restrictions [4] on April 7, 2 mo after raising the national Disease Outbreak Response System Condition (DORSCON) level from yellow to orange [5], and 1 mo after lockdown in Italy. We reviewed urology admissions via the ED, excluding non-admitted patients (as our ED has consistent admission criteria), divided into three groups according to important national timelines: group A (heightened surveillance period) from January 3 to February 6 (35 d), group B (1 st month of DORSCON orange level) from February 7 to March 6 (29 d), and group C (2nd month of DORSCON orange level) from March 7 to April 6 (31 d). At the time of writing, data after the "circuit breaker" restrictions are unavailable.

Group A included 109 patients (3.11 patients/d), group B 83 (2.86 patients/d), and group C 66 (2.22 patients/day). Urolithiasis cases accounted for 24 patients in group A (22.02%), with a decrease to 12 in group B (14.46%) and 12 (18.18%) in group C. Genitourinary infections remained the most common diagnosis, increasing in percentage despite increasing COVID-19 concerns: 39 in group A (35.78%), 46 in group B (55.42%), and 35 in group C (53.03%).

The second issue, brought to the surface by this pandemic, of possible chronic abuse of hospital resources by low-complexity cases is a sensitive one. A review of our data set revealed that the decrease in urolithiasis consultations reported by Mantica et al is similar to our reduction in urolithiasis admissions. We postulate that during the COVID-19 pandemic, Singapore patients were preferentially seeking conservative care in the community or deferring consultations. This is in contrast to the higher percentage of haematuria cases noted by Mantica et al, similar to the higher percentage of genitourinary infections we observed, as these conditions can seldom be deferred. Importantly, we must further analyse if this percentage rise in infections and haematuria is a consequence of delayed health-seeking behaviour or of failed treatment in the community. Our data set is unable to definitively determine if ED abuse was the case, but with rigorous admission criteria we can prevent unnecessary admissions and preserve inpatient resources.

COVID-19 will have a long-lasting impact on health care and urological practice will be no exception. These observations remind urologists of the importance of our nations' health care policies to establish an integrated system of primary, emergency, and tertiary care so that patients can access essential care in the community, even during crises. If urologists act quickly in anticipating post-COVID-19 issues and in using this pandemic to review reforms for our health care systems, we can emerge stronger than before.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Chan MC, Yeo SEK, Chong YL, Lee YM. Stepping Forward: Urologists' Efforts During the COVID-19 Outbreak in Singapore. Eur Urol 2020;78:e38–9.
[2] Stensland KD, Morgan TM, Moinzadeh A, et al. Considerations in the Triage of Urologic Surgeries During the COVID-19 Pandemic. Eur Urol 2020;77:663–6.
[3] Proietti S, Gaboardi F, Giusti G. Endourological Stone Management in the Era of the COVID-19. Eur Urol 2020;78:131–3.

DOI of original article: https://doi.org/10.1016/j.eururo.2020.04.045.
https://doi.org/10.1016/j.eururo.2020.04.071

[4] Ministry of Health Singapore. Circuit breaker to minimise further spread of COVID-19. www.moh.gov.sg/news-highlights/details/circuit-breaker-to-minimise-further-spread-of-covid-19.
[5] Government of Singapore. What do the different DORSCON levels mean. www.gov.sg/article/what-do-the-different-dorscon-levels-mean.

Ming-Chun Chan[a,*]
Sharon E.K. Yeo[a,b]
Yew-Lam Chong[a,b,c]
Yee-Mun Lee[a,b]

[a]*Department of Urology, Tan Tock Seng Hospital, Singapore*
[b]*Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*
[c]*Yong Loo Lin School of Medicine, National University Singapore, Singapore*

[*]Corresponding author. Department of Urology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433 Singapore. Tel. +65 98289877, Fax: +65 6889 4260.
E-mail address: mingchunchan@hotmail.com (M.-C. Chan).

April 30, 2020