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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

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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
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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
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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
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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
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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.2021.06.016

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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

2021

The DaBlaCa-13 Study: Short-term, Intensive Chemoresection Versus Standard Adjuvant Intravesical Instillations in Non–muscle-invasive Bladder Cancer—A Randomised Controlled Trial

Maria S. Lindgren, Peter Bue, Nessn Azawi, Linea Blichert-Refsgaard, Maria O. Sundelin, Lars Dyrskjø, Jørgen B. Jensen

European Urology, Vol 78, Issue 6, p856–862

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

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

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European Urology 2007;52:798–803

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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

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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

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

2021

Gut Bacteria Composition Drives Primary Resistance to Cancer Immunotherapy in Renal Cell Carcinoma Patients
Lisa Derosa, Bertrand Routy, Marine Fidelle, Valerio Iebba, Laurie Alla, Edoardo Pasolli, Nicola Segata, Aude Desnoyer, Filippo Pietrantonio, Gladys Ferrere, Jean-Eudes Fahrner, Emmanuelle Le Chatellier, Nicolas Pons, Nathalie Galleron, Hugo Roume, Connie P.M. Duong, Laura Mondragón, Kristina Iribarren, Mélodie Bonvalet, Safae Terrisse, Conrad Rauber, Anne-Gaëlle Goubet, Romain Daillère, Fabien Lemaitre, Anna Reni, Beatrice Casu, Maryam Tidjani Alou, Carolina Alves Costa Silva, Didier Raoult, Karim Fizazi, Bernard Escudier, Guido Kroemer, Laurence Albiges, Laurence Zitvogel
European Urology, Vol 78, Issue 2, p195-206

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
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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

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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

2021

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"

Marc-Oliver Grimm, Antoine G. van der Heijden, Marc Colombel, Tim Muilwijk, Luis Martínez-Piñeiro, Marko M. Babjuk, Levent N. Türkeri, Joan Palou, Anup Patel, Anders S. Bjartell, Christien Caris, Raymond G. Schipper, Wim P.J. Witjes for the EAU Research Foundation NIMBUS Study Group

European Urology, Vol 78, Issue 5, p690-698

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

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European Urology 2008;54:1354–1362

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Platinum Opinion

Treatment and Patient Selection for Patients with Metastatic Castration-resistant Prostate After Progression on Docetaxel and Abiraterone/Enzalutamide: When to Play Your CARD and When to Do Your PARP

Andrew G. Robinson [a], *Jason P. Izard* [b], *Francisco E. Vera-Badillo* [a,*]

[a] *Division of Medical Oncology, Department of Oncology, Queen's University, Kingston, ON, Canada;* [b] *Department of Urology, Queen's University, Kingston, ON, Canada*

For patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after an androgen receptor axis–targeted therapy (ARAT) and docetaxel, two different alternatives have shown promise in phase 3 clinical trials: a "targeted" strategy using poly (ADP-ribose) polymerase (PARP) inhibitors and a "nontargeted" chemotherapy strategy using cabazitaxel. As of yet, there is no direct randomized evidence to compare PARP inhibitors to cabazitaxel. Here we address the sequencing to consider when possibly integrating these drugs into practice. Table 1 lists details of the studies discussed.

The efficacy of cabazitaxel compared to mitoxantrone after failure on docetaxel was initially demonstrated in a randomized trial [1]. A median improvement in overall survival (OS) of 2.4 mo (hazard ratio [HR] 0.70; $p < 0.0001$) was achieved. US Food and Drug Administration (FDA) approval was obtained in 2010. However, the use of cabazitaxel was rapidly displaced by ARAT. In September 2019 the CARD investigators reported the results of a randomized study addressing whether cabazitaxel still provided a benefit as a third-line agent after progression on docetaxel and one ARAT [2] compared to the ARAT agent not previously used. The primary endpoint for the CARD study was radiographic progression-free survival (rPFS) and OS was a secondary endpoint. There was a significant improvement in rPFS of 8.0 versus 3.7 mo favoring cabazitaxel (HR 0.54; $p < 0.001$). OS was also statistically superior with cabazitaxel (13.6 vs 11.0 mo, HR 0.64; $p = 0.008$).

As the CARD study was not designed to select participants by biomarker expression, any patient progressing after treatment with docetaxel and an ARAT should be considered an appropriate candidate for this intervention. However, there were some caveats in this trial. First, by including only patients who progressed on a previous ARAT within 12 mo, the study selected a group of patients who were less likely to respond to a second ARAT challenge. The median duration of therapy in the COU-AA-302 and PREVAIL trials was 13.8 and 16.6 mo, respectively [3,4]. Use of cabazitaxel in patients with longer durations of a previous ARAT benefit may be a reasonable extrapolation of the evidence in some select cases. Second, the cabazitaxel dose used in this trial was 25 mg/m^2, which requires the use of colony-stimulating factor support. The 20 mg/m^2 dose has been adopted worldwide because of its equivalent efficacy and more manageable toxicity [5].

In contrast to cabazitaxel, PARP inhibition represents a "targeted" approach to mCRPC treatment. Two PARP inhibitors, olaparib and rupacarib, have been approved for patients who have progressed on docetaxel and whose tumors harbor deleterious aberrations in DNA repair genes. It has been reported that these deleterious aberrations are present in up to 30% of patients with mCRPC [6]. Among the most common genes altered are *BRCA1* and *BRCA2*. It is believed that such gene alterations confer sensitivity to PARP inhibition [7].

On May 19, 2020, on the basis of results from the phase 3 PROFOUND trial [8], the FDA approved olaparib for patients

* Corresponding author. Department of Oncology, Queens University, 25 King Street West, Kingston, Ontario K7L 598, Canada. Tel. +1 613 5496666; Fax: +1 613 5468201.
E-mail address: francisco.verabadillo@kingstonhsc.ca (F.E. Vera-Badillo).

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Table 1 – Study characteristics

	TOPARP-A	TOPARP-B	PROfound	Study 08	TRITON-2	GALAHAD	CARD
Experimental agent	Olaparib	Olaparib	Olaparib	Olaparib	Rucaparib	Niraparib	Cabazitaxel
FDA status	–	–	Approved	–	Approved	Breakthrough designation	Approved
Status	Published	Published	Published	Published	Published	Abstract	Published
Median follow-up (mo)	14.4	24.8	12.2	15.9	17.1	7.3	9.2
Phase	Phase 2	Phase 2	Phase 3	Phase 2	Phase 2	Phase 2	Phase 3
Arms	Single: Ola 400 mg bid	Randomized: Ola 300 and 400 mg bid	Randomized: Ola 300 mg bid vs Enza/Abi	Randomized: Ola 300 mg bid vs Pbo (both in combination with Abi + prednisone)	Rucaparib 600 mg bid	Niraparib 300 mg once daily	
Successfully screened (*n*)	49	711	2792	142	NA	223	129 (Caba)
							126 (ARAT)
BM +ve, *n* (%)	16 (32)	161 (23)	778 (28)	All comers	115	165 (74)	NA
DNA damage repair genes	*BRCA1/2*, ATM, *FANCA*, *CHECK2*, *PALB2*, *HDAC2*, *RAD51*, *MLH3*, *ERCC3*, *MRE11*, *NBN*		Cohort A: *BRCA1/2*, *ATM*	NA	*BRCA1/2*	*BRCA1/2*, *ATM*, *FANCA*, *PALB2*, *CHEK2*, *BRIP1*, *HDAC2*	NA
			Cohort B: *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*				
BM +ve patients included in primary analysis, *n* (%)		92 (13)	387 (14)	NA	65 in IEP	51 (36)	NA
					62 in IRRP		
Previous docetaxel (%)	100	100	45	100	CRPC: 94	100	100
					CSPC: 17		
Previous Enza or Abi (%)	100	88–92 (Enza, Abi or both)	41	1	Abi: 64	100	43–56 (Caba)
					Enza: 71		47–53 (ARAT)
Previous Abi and Enza (%)	NR	NR	20 (Ola)	NA	36	NR	NR
			18 (control)				
Previous Caba (%)	58	31–45	20	14	8	NR	NA
RR overall (%) [a]	88	47	21.7	27 (vs 32 Pbo + Abi)	44 [d]	NR	36
RR *BRCA1/2* (%)	100	83	33 [b]	13.8 (Ola + Abi)	44	63	NA
				8.2 (Pbo + Abi)			
RR other mutation (%)	78	20-57	3.7 [c]	22.7 (Ola + Abi)	–	17	NA
				20.9 (Pbo + Abi)			
rPFS (mo)	9.8 (BM +ve)	5.5 (400 mg bid)	7.4 (Olaparib) [b]	13.8 (Ola + Abi)	9.0	8.2 (5.3 non-BRCA)	8.0 (Caba)
	2.7 (BM –ve)	5.6 (300 mg bid)	3.6 (control)	8.2 (Pbo + Abi)			3.7 (ARAT)
Overall survival (mo)	13.8 (BM +ve)	14.3 (400 mg bid)	19.1 (Ola) [b]	22.7 (Ola + Abi)	NR	12.6 (14 non-BRCA)	13.6 (Caba)
	7.5 (BM –ve)	10.1 (300 mg bid)	14.1 (control)	20.9 (Pbo + Abi)			11.0 (ARAT)

Abi = abiraterone; ARAT = androgen receptor axis–targeted; bid = twice daily; BM = biomarker; Caba = cabazitaxel; CRPC = castration-resistant prostate cancer; CSPC = castration-sensitive prostate cancer; Enza = enzalutamide; FDA = US Food and Drug Administration; IEP = investigator evaluable population; IRRP = independent radiology review population; Ola = olaparib; NA = not applicable; NR = not reported; Pbo = placebo; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; rPFS = radiographic progression-free survival; RR = response rate.

[a] RR is defined as a response according to RECIST 1.1, a reduction in PSA level of ≥50%, or conversion of circulating tumor cell count, indicated by a reduction in the number of circulating tumor cells from ≥5/7.5 ml of blood at baseline to <5/7.5 ml during treatment, with a confirmatory assessment at least 4 wk later.

[b] Includes *ATM*.

[c] Does not include *ATM*.

[d] Only patients with *BRCA1/2* mutation were enrolled. RR was defined as per RECIST 1.1/Prostate Cancer Working Group 3 or PSA level ≥50%.

with mCRPC with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutations who have progressed following prior treatment with enzalutamide or abiraterone.

The activity of olaparib in mCRPC has been demonstrated in two phase 2 and one phase 3 trials. In the PROfound trial [8], patients were enrolled in two experimental cohorts. Cohort A (245 patients) comprised those carrying at least one alteration in *BRCA1*, *BRCA2*, or *ATM*. Cohort B (142 patients) comprised those with alterations in any of 12 other prespecified genes. The primary endpoint was rPFS in cohort A. Patients may have had prior chemotherapy, but this was not mandated, and patients who had not received either docetaxel or cabazitaxel were included. Patients who had received abiraterone and/or enzalutamide were allowed to enroll in the trial and received a second ARAT if they were in the control arm, and may have even received an ARAT that they previously progressed on. Results showed a significant improvement in rPFS for cohort A (HR 0.34; $p < 0.001$) and the combination of cohorts A and B (HR 0.49; $p < 0.001$). There was also an significant improvement in median OS for cohort A of 4.4 mo (19.1 vs 14.7 mo, HR 0.69; $p = 0.02$) [9]. For cohort B only, no clear evidence of a benefit for rPFS (HR 0.88) or OS (HR 0.96) was found. When different gene alteration groups were assessed, the only alteration that remained statistically significant was *BRCA2* (HR 0.21). Mutations in *BRCA1*, *ATM*, and the genes included for cohort B did not significantly improve rPFS. However, the study was underpowered for showing a significant difference for the rarer gene alterations; for example, only 4% of the overall cohort had a *BRCA1* mutation.

Caveats for the PROfound trial are very important to highlight, as the trial design can potentially affect the interpretation of the results. One major concern is the validity of the control arm. Some 17% of the control group had received both ARATs (enzalutamide and abiraterone) and were rechallenged with a drug that they had previously progressed on. The other important issue to address is the use of an alternative ARAT in the second line after previous progression on an ARAT. For these patients, we would expect a limited response rate to the second-line ARAT and a limited duration of response in those who do respond. As reported for the CARD trial, the best approach is to use a different mechanism of action such as chemotherapy. The enrollment of patients who had not received standard therapy (docetaxel) is concerning, as only 56% of patients had received prior docetaxel (with or without subsequent cabazitaxel). Therefore, 44% of the patients were enrolled had never been exposed to a treatment that has been assessed as a modestly effective intervention that improves not only quality of life but also OS.

On May 15, 2020, rucaparib received accelerated approval for treatment of patients with mCRPC and a deleterious *BRCA1/2* alteration who have been treated with androgen receptor directed–therapy and taxane-based chemotherapy. This approval was based on the objective response rate and duration of response observed in the multicenter, single-arm TRITON2 trial [10]. In this trial, a high proportion of patients had received abiraterone (64%) and enzalutamide (71%) and nearly all patients had received docetaxel. Complete and partial responses were achieved in 11% and 32% of patients, respectively. Prostate-specific antigen (PSA) responses were seen in 55% of the patients. Radiographic response rates were independent of *BRCA1* or *BRCA2* alterations, although the group with *BRCA2* alterations did exhibit a higher PSA response rate (60% vs 15%).

Niraparib has also shown efficacy among patients with mCRPC who were biomarker-positive for HRR and had progressed on ARAT and taxane-based chemotherapy [11]. Among the 51 patients, 29 had *BRCA1/2* alterations and 22 had non-*BRCA* alterations. The difference in response rate favored the *BRCA1/2* group (41% vs 9%). On the basis of this trial, the FDA granted breakthrough designation for review.

There is no doubt that these agents can provide a significant impact on OS for patients for whom standard regimens have failed. However, it is crucial to narrow the potential patient population for exposure to these drugs to maximize the chances of response. In the past we have lamented the lack of biomarkers available to guide decision-making. In this instance we have too many biomarkers and further dissection of the data is needed to elucidate which HRR alterations predict a meaningful response to these agents. We suggest that only patients with expression of a *BRCA2* alteration should receive a PARP inhibitor, and docetaxel or cabazitaxel should be favored when *BRCA2* alterations are not present, provided the patient is naïve to these drugs. Highly symptomatic patients in whom a fast response for palliative purposes is desirable might be considered more suitable candidates for chemotherapy. For patients progressing on a PARP inhibitor, further chemotherapy can be considered as an acceptable treatment option if their performance status allows for this type of intervention. The role of platinum agents for patients with *BRCA1/2* alterations still needs to be defined.

Conflicts of interest: The authors have nothing to disclose.

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Platinum Opinion

Virtual Conferences and the COVID-19 Pandemic: Are We Missing Out with an Online Only Platform?

Phillip Woodruff[a,b], *Christopher J.D. Wallis*[c], *Peter Albers*[d], *Zachary Klaassen*[a,e,*]

[a] *Division of Urology, Department of Surgery, Medical College of Georgia, Augusta University, Augusta, GA, USA;* [b] *St. George's University School of Medicine, St. George's, Grenada;* [c] *Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA;* [d] *Department of Urology, University Hospital Düsseldorf, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany;* [e] *Georgia Cancer Center, Augusta, GA, USA*

For centuries, medical conferences have been a primary modality for disseminating and presenting new research. As a result of the COVID-19 pandemic, this model has been dramatically disrupted: without established precedent in many cases, the traditional conference approach dramatically adjusted from initial cancellations (particularly early in the pandemic) to a virtual approach now used by the majority of scientific meetings held this year. While this change is associated with lower travel expenses, a positive environmental impact, and convenient access to content [1], there are many potential pitfalls, including a decrease in social networking (which may disproportionately affect junior physicians), fewer ad hoc discussions and resultant collaborations, a potential decrease in interactivity and engagement, and loss of the social component of conference participation [2]. In light of these effects, we wondered how the transition to a virtual format affects interest in conferences.

In a recent Twitter poll conducted *by European Urology* (@EUplatinum), followers were asked "As we round out 2020 and the ongoing pandemic: Are you more or less likely to submit an abstract to a conference if the meeting is going to be virtual?" The majority of respondents indicated that they would be less likely to submit to a virtual conference (54%, Fig. 1). With clinicians and researchers less inclined to submit their work to strictly virtual conferences, the ramifications of these "lost opportunities", from the perspectives of both a research dissemination and in-person fostering of research/mentoring collaborations, remain to be determined.

Virtual conferences are arguably less likely to negatively affect the reporting of results from important phase 2/3 clinical trials. The recent 2021 virtual genitourinary

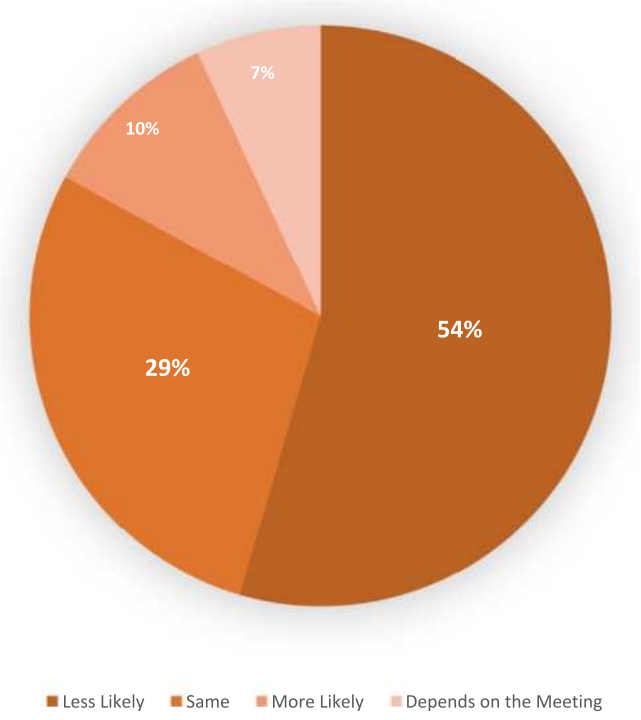

Fig. 1 – Pie chart depicting results of an @EUplatinum Twitter poll on December 16, 2020 assessing the impact of strictly virtual conferences on the likelihood of submitting research abstracts.

American Society of Clinical Oncology (GU ASCO) meeting marked 1 yr since urology/major oncology meetings were forced to adopt a completely virtual platform. Despite the virtual platform, GU ASCO 2021 saw the reporting and

* Corresponding author. Georgia Cancer Center, 1120 15th Street, Augusta, GA 30912, USA. Tel. +1 706 7212519; Fax: +1 706 7212548.
E-mail address: zklaassen@augusta.edu (Z. Klaassen).

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publication of two *New England Journal of Medicine* [3,4] and two *Lancet* [5,6] trials in prostate, kidney, and urothelial carcinoma. However, fewer submissions to virtual conferences may lead to fewer presentations of studies not funded by pharmaceutical companies, including observational and post hoc analyses of clinical trials, which are often presented by residents, fellows, and trainees. While much of the important data from these studies will eventually be published in peer-reviewed journals, a large proportion will not [7] and the loss of these academic opportunities for junior physicians probably extends beyond the dissemination of their data.

This transition to virtual meetings has probably also hampered professional development, particularly for individuals in medical training. First, research productivity and the associated conference presentations are a key component of applications for residency and fellowship. These presentations reflect the trainees' research acumen, critical thinking skills, and presentation ability. The loss of in-person conferences will diminish opportunities to hone public speaking skills. Furthermore, there is a loss of the opportunity to present and interact with an audience, providing lessons in answering questions, taking feedback, and defending one's research, not to mention the exposure granted by these presentations. The ad hoc spontaneous networking opportunities afforded by in-person conferences cannot easily be replicated in a virtual setting. Thus, opportunities for collaboration, mentorship, and generating new ideas for clinicians, researchers, and medical trainees are probably lost.

The results of the @EUplatinum Twitter poll demonstrate that with 1 yr of experience with virtual medical conferences necessitated by the COVID-19 pandemic, *European Urology* followers are much less interested in contributing to conferences held virtually. This is important in the context of the upcoming European Association of Urology annual meeting, which was recently changed to an entirely virtual format from the planned hybrid meeting to be held in Milan, Italy. With increasing uptake and availability of COVID-19 vaccines, a return to in-person urology conferences is probably not far off. The utilization of virtual formats has allowed for wide dissemination of conferences in real time, including increased participation by virtual attendees from South America and China, and wider dissemination of knowledge to countries with lower income, a valuable goal we need to maintain in the future. However, the enthusiasm, networking, collaborations, and social gatherings that come with in-person conferences are uniquely valuable in the academic world. Thoughtful adoption of hybrid meetings may allow the urology community to reap the benefits of each of these approaches for many years after the COVID-19 pandemic subsides.

Conflicts of interest: The authors have nothing to disclose.

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Brief Correspondence

Impact of the Implementation of the EAU Guidelines Recommendation on Reporting and Grading of Complications in Patients Undergoing Robot-assisted Radical Cystectomy: A Systematic Review

Paolo Dell'Oglio[a,b,c,*], *Iulia Andras*[d], *David Ortega*[e], *Antonio Galfano*[a], *Walter Artibani*[f], *Riccardo Autorino*[g], *Elio Mazzone*[h], *Nicolae Crisan*[d], *Aldo Massimo Bocciardi*[a], *Rafael Sanchez-Salas*[i], *Inderbir Gill*[e], *Peter Wiklund*[j], *Mihir Desai*[e], *Dionysios Mitropoulos*[k], *Alexandre Mottrie*[l,m], *Giovanni E. Cacciamani*[e,**]

[a] *Department of Urology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;* [b] *Department of Urology, Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [c] *Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands;* [d] *Department of Urology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania;* [e] *University of Southern California Institute of Urology & Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [f] *Department of Urology, University of Verona, Verona, Italy;* [g] *Division of Urology, Department of Surgery, VCU Health System, Richmond, VA, USA;* [h] *Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [i] *Department of Urology, Institut Mutualiste Montsouris, Paris, France;* [j] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [k] *1st Department of Urology, University of Athens Medical School, Athens, Greece;* [l] *Department of Urology, Onze Lieve Vrouw Hospital, Aalst, Belgium;* [m] *ORSI Academy, Melle, Belgium*

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Abstract

In 2012, the European Association of Urology (EAU) Ad Hoc Panel proposed a standardised methodology on reporting and grading complications after urological surgical procedures. The aim of the current study was to assess the impact of this implementation on complications reporting for patients undergoing robot-assisted radical cystectomy (RARC). A systematic review of all English-language original articles published on RARC until March 2020 was performed using PubMed, Scopus, and Web of Science databases. The study selection process followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) criteria. The quality of reporting and grading complication was evaluated according to the EAU recommendations. Our analysis failed to observe a statistically significant improvement in reporting outcomes after the EAU guidelines recommendations except for three of the 14 criteria proposed (ie, follow-up

* Corresponding author. Department of Urology, ASST Grande Ospedale Metropolitano Niguarda, Milan Italy; Department of Urology, Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands. Tel. +39 02 6444 4617; Fax: +39 02 6444 7896.
E-mail addresses: paolo.delloglio@gmail.com (P. DellOglio), giovanni.cacciamani@med.usc.edu (G.E. Cacciamani).

** Corresponding author. Department of Urology, University of Southern California, Los Angeles, CA, USA; Department of Radiology, University of Southern California, Los Angeles, CA, USA; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA.
E-mail address: giovanni.cacciamani@med.usc.edu (G.E. Cacciamani).

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duration, utilisation of a severity grade system, and risk factors included in the analyses). A lower statistically significant adherence to outcome reporting in terms of inclusion of readmissions and causes (p = 0.02), was observed.
Patient summary: In this study, we evaluated the impact of the proposed European Association of Urology (EAU) standardised reporting tool for urological complications, in patients treated with robot-assisted radical cystectomy. A low adherence to EAU guidelines recommendations for complications reporting was observed.

Robot-assisted radical cystectomy (RARC) is a complex surgical procedure associated with a non-negligible learning curve [1] and a postoperative morbidity that ranges between 26% and 78% [2]. This heterogeneous rate of complications might be explained, in part, by the variability in the definition and reporting of complications. Indeed, despite morbidity representing one of the pivotal surgical outcomes [3], so far no universally accepted criteria for an accurate measurement exist in the urological field. In 2012, the European Association of Urology (EAU) Ad Hoc Panel proposed a standardised methodology on reporting and grading complications after surgical procedures that relied on 14-item criteria [4]. This standardised reporting tool was validated in a series of patients who underwent robot-assisted radical prostatectomy [5], and it was observed that the tool's implementation increased the detection rate of complications relative to a collection system based on patient chart review and allowed for the identification of complications after discharge that would have been missed. This is a clear demonstration of the concept that "what you measure depends on the tool you use" [6,7] and that standardised and rigorous tools are mandatory to avoid reporting unreliable data.

The aim of the current study was to assess the impact of the implementation of the EAU guidelines recommendations on reporting and grading of complications for patients undergoing RARC.

A systematic literature search was performed on the MEDLINE/PubMed, Scopus and Web of Science databases to identify all English-language original articles published between January 2004 and March 2020. Only those articles reporting complications as an outcome of interest were included. The study selection process is outlined in a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1).

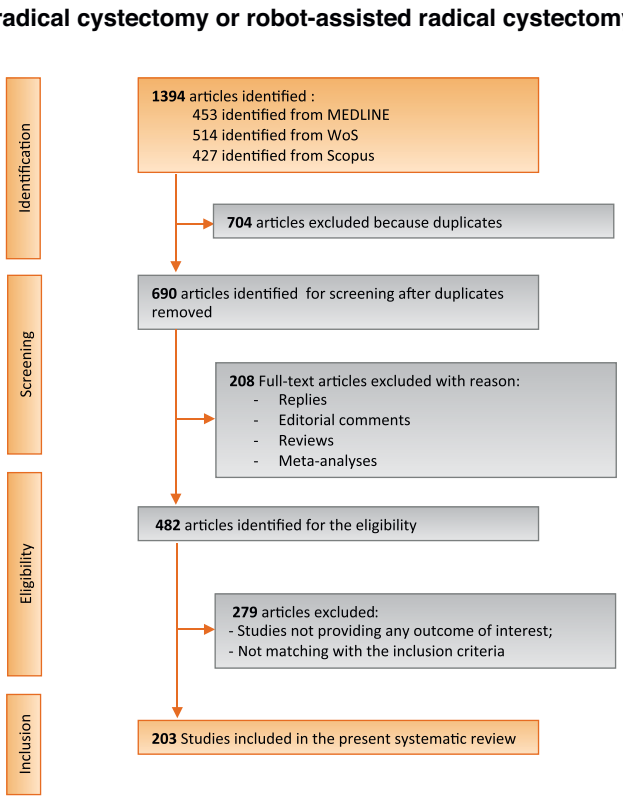

Fig. 1 – PRISMA flow chart for the selection of papers on robot-assisted radical cystectomy published in English up to March 2020. PRISMA = Preferred Reporting Items for Systematic Review and Meta-analyses; WoS = Web of Science. Literature search strategy: (robotic radical cystectomy or robot-assisted radical cystectomy) and complication

Table 1 – Comparison of quality assessment criteria before and after the European Association of Urology guidelines recommendations

	Before EAU recommendations	After EAU recommendations	*p* value
No. of studies reporting complications	48	155	
Type of criteria satisfied			
1. Method of accruing data defined	6 (12.5%)	36 (23.2%)	0.2
2. Who collected the data defined	2 (4.2%)	8 (5.2%)	0.9
3. Duration of follow-up indicated	34 (70.8%)	143 (92.3%)	<0.001
4. Outpatient information included	11 (22.9%)	52 (33.5%)	0.2
5. Mortality rate and causes of death listed	18 (37.5%)	65 (41.9%)	0.7
6. Definition of complications provided	8 (16.7%)	21 (13.5%)	0.8
7. Procedure-specific complications included	38 (79.2%)	102 (65.8%)	0.1
8. Separate reporting of intra- and postoperative complications	14(29.2%)	25 (16.1%)	0.07
9. Severity grade used	26 (54.2%)	145 (93.5%)	<0.001
10. Postoperative complications presented in a table either by grade or by complication type	25 (52.1%)	99 (63.9%)	0.2
11. Risk factors included in analysis (ASA, Charlson)	32 (66.7%)	132 (85.2%)	0.008
12. Readmissions and causes included	12 (25%)	16 (10.3%)	0.02
13. Reoperations, types, and causes included	18 (37.5%)	44 (28.4%)	0.3
14. Percentage of patients lost to follow-up included	1 (2.1%)	10 (6.5%)	0.4

ASA = American Society of Anesthesiologists; EAU = European Association of Urology.

The systematic review protocol was registered in PROSPERO (CRD42021231699). The quality criteria for accurate and comprehensive reporting of surgical outcomes recommended by the EAU guidelines on reporting and grading of complications were fulfilled for the studies assessed [4]. To establish a possible change in attitude towards the reporting of complications, temporal comparisons were performed for reports before and after the introduction of the EAU guidelines on complication reporting in 2012. Data for categorical variables are shown as percentages, and differences between groups were analysed using the McNemar test. For all statistical analyses, R software environment for statistical computing and graphics (version 3.6.3) was used, and all tests were two sided with significance level set at $p < 0.05$.

Overall, 203 studies were identified (Fig. 1 and Supplementary Table 1). Of these studies, 24% (n = 48) and 76% (n = 155) were published, respectively, before and after the EAU Ad Hoc Panel recommendations for reporting and grading complications. None of these studies fulfilled all the 14 criteria. Overall, 79% (38/48) and 79% (123/155) of the articles published, respectively, before and after EAU guidelines recommendations met seven or fewer criteria. No statistically significant differences were observed in terms of the definition of method for accruing data (12.5% vs 23.2%), identification of the person or organisation that collected the data (4.2% vs 5.2%), outpatient information (22.9% vs 33.5%), mortality rate and cause of death (37.5% vs 41.9%), definition of complications (16.7% vs 13.5%), inclusion of procedure-specific complications (79.2% vs 65.8%), separate reporting of intra- and postoperative complications (29.2% vs. 16.1%), postoperative complications reported in a table either by grade or by complication type (52.1% vs 63.9%), reoperation types and causes reported (37.5% vs 28.4%), and percentage of patients lost to follow-up (2.1% vs 6.5%) were observed, when we compared the quality of reporting criteria before and after the introduction of the EAU guidelines on complication reporting (Table 1 and Fig. 2). Conversely, significant improvement was observed for indication of follow-up duration (70.8% vs 92.3%), utilisation of a severity grade system (54.2% vs 93.5%), and risk factors included in the analyses (66.7% vs 85.2%) after EAU guidelines recommendations. Instead, we observed statistically significant differences in terms of inclusion of readmissions and causes (25% vs 10.3%) in favour of the articles published before 2012.

Our findings revealed that, despite the increasing number of RARC studies published over time, none of the available articles fulfilled all the 14 criteria proposed by the EAU panel for reporting and grading of complications, and the majority (79% and 79% before and after EAU recommendations, respectively) are reporting complications relying on ≤50% of the recommended criteria. Moreover, we failed to observe an improvement in reporting outcomes, except for three of the 14 criteria (ie, follow-up duration, utilisation of a severity grade system, and risk factors included in the analyses). A lower statistically significant adherence to one of the 14 criteria proposed was identified after 2012. Specifically, we recorded a reduction of 15% for inclusion of readmission and causes. Furthermore, a decrease, despite not being statistically significant, was observed for four criteria, namely, definition of complications, inclusion of procedure-specific complications, separate reporting of intra- and postoperative complications and inclusion of reoperation types and causes. Of note, nine of 14 criteria were under-reported (≤50%) after the EAU recommendation, and the majority of the RARC studies did not assess who collected the data and did not report the percentage of patients lost to follow-up.

Overall, our findings suggested that the scientific community is not widely adhering to the 14-item standardised reporting tool proposed by the EAU panel in 2012. This low adherence to EAU guidelines recommendations could impact the quality of data [6] published on RARC complications. On the contrary, the indication of the follow-up duration, utilisation of a severity grade system such as the Clavien-Dindo system, and inclusion of risk factors in the analysis increased after the EAU panel

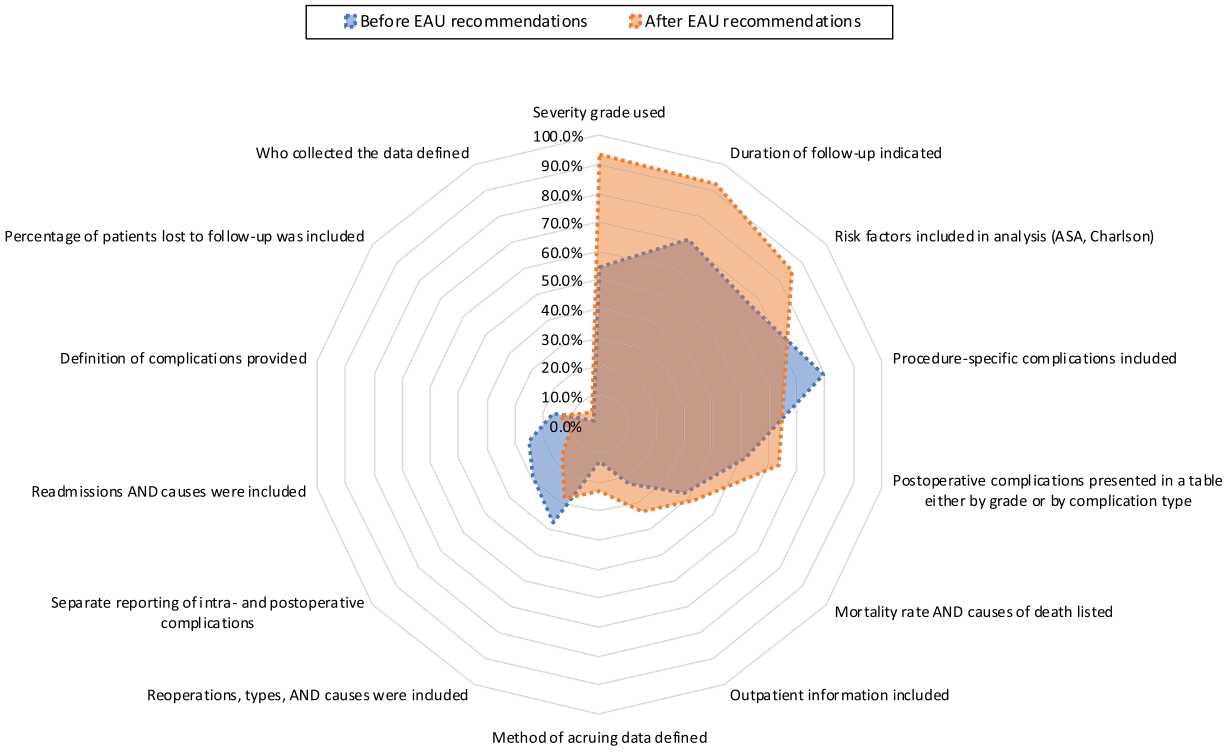

Fig. 2 – Comparison of quality assessment criteria following the EAU guidelines recommendations. ASA = American Society of Anesthesiologists; EAU = European Association of Urology.

recommendations. Nevertheless, these three criteria alone could not be sufficient to depict the adverse events related to RARC. With the reduction of the length of stay related to minimally invasive surgery, a significant proportion of postoperative complications occur after hospital discharge [8]. Therefore, other criteria such as outpatient information and readmission rate become crucial [5,9]. From a clinical point of view, this will have remarkable consequences considering the fact that urological international guidelines are built on available evidence. As there was a great consensus and a lot of efforts were made to create a standardised reporting tool for reporting urological complications to avoid misleading information, clinicians should pay more attention to providing and accepting original articles in which the quality of reporting and grading complications is not assessed according to EAU recommendations. At the same time, our findings could help clinicians evaluate their own RARC complication reporting and advise authors of future manuscript to improve complication reporting, implementing the EAU ad hoc criteria in the prospective data collection setting. Differently from the RARC setting, recent data observed that these recommendations led to an improvement in reporting complications after robot-assisted partial nephrectomy [10].

To conclude, our results urgently call for a rigorous use of standardised methodology to collect perioperative outcomes [4] in RARC setting in order to allow proper interpretation of surgical outcomes, to avoid missing critical information that could lead to an underestimation of perioperative complications and to improve patient counselling regarding the adverse events related to RARC.

Available literature reveals important heterogeneity in adverse event assessment and reporting after RARC, calling for an impending need to adopt standardised criteria to accurately assess surgical performance, and portray the risk and benefit of RARC during preoperative counselling, minimising regrets and maximising satisfaction.

***Author contributions*:** Paolo Dell'Oglio and Giovanni Cacciamani 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: Dell'Oglio, Cacciamani.
Acquisition of data: Dell'Oglio, Andras, Ortega, Cacciamani.
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Appendix A. Supplementary data

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Platinum Priority Brief Correspondence – Editor's Choice

Editorial by Jianfeng Xu and William B. Isaacs on pp. 139–141 of this issue

Combined Effect of a Polygenic Risk Score and Rare Genetic Variants on Prostate Cancer Risk

Burcu F. Darst [a,*], ***Xin Sheng*** [a], ***Rosalind A. Eeles*** [b,c], ***Zsofia Kote-Jarai*** [b], ***David V. Conti*** [a], ***Christopher A. Haiman*** [a]

[a] *Center for Genetic Epidemiology, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA, USA;* [b] *The Institute of Cancer Research, London, UK;* [c] *The Royal Marsden NHS Foundation Trust, London, UK*

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Abstract

Although prostate cancer is known to have a strong genetic basis and is influenced by both common and rare variants, the ability to investigate the combined effect of such genetic risk factors has been limited to date. We conducted an investigation of 81 094 men from the UK Biobank, including 3568 prostate cancer cases, to examine the combined effect of rare pathogenic/likely pathogenic/deleterious (P/LP/D) germline variants and common prostate cancer risk variants, measured using a polygenic risk score (PRS), on prostate cancer risk. The absolute risk of prostate cancer for *HOXB13*, *BRCA2*, *ATM*, and *CHEK2* P/LP/D carriers ranged from 9% to 56%, and the absolute risk in noncarriers ranged from 2% to 31%, by age 85 yr, for men in the lowest and highest PRS decile, respectively. The high-penetrant *HOXB13* G84E prostate cancer risk variant was most common in cases in the lowest PRS quintile (4.4%) and least common in cases in the highest PRS quintile (0.5%; $p = 0.005$), whereas there was no statistically significant difference in frequencies by PRS in controls. While rare and common variants strongly and distinctly influence prostate cancer onset, consideration of rare and common variants in conjunction will lead to more precise estimates of a man's lifetime risk of prostate cancer.

Patient summary: We found that the risk of prostate cancer conveyed by rare variants could vary depending on an individual's genetic profile of common risk variants. This implies that in order to comprehensively assess genetic risk of prostate cancer, it is important to consider both rare and common variants.

* Corresponding author. Center for Genetic Epidemiology, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, 1450 Biggy Street, Los Angeles, CA 90033, USA. Tel. +1 232 442 0078; Fax: +1 323 442 0078.
E-mail address: bdarst@usc.edu (B.F. Darst).

Prostate cancer (PCa) is a leading cause of death, with high heritability and risk among family members suggesting a strong genetic basis of this disease [1,2]. Rare germline genetic variants have been shown to increase PCa risk [3,4], as have common variants in aggregate as measured by polygenic risk scores (PRSs), with men in the highest PRS decile having approximately four-fold increased odds of PCa than men in the average 40–60% PRS category [5]. Until recently, the ability to investigate the combined influence of rare and common variants has been limited. Recent studies

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0302-2838/

have shown that common variants modify the influence of rare variants on breast cancer, colorectal cancer, and coronary artery disease risk [6,7], and the influence of rare *BRCA2* and *HOXB13* variants on PCa risk has been shown to vary by common variants [8–10]. Here, we investigated the combined effect of rare and common germline variants on PCa risk using whole-exome sequencing and genome-wide genotype data in a large sample of 81 094 European ancestry men from the UK Biobank (October 2020 release of 200K whole-exome sequences), including 3568 PCa cases and 77 526 controls.

We first performed exome-wide gene-based analyses to determine whether novel PCa risk genes could be identified from rare pathogenic/likely pathogenic/deleterious (P/LP/D) variants. Across 14 905 tested genes, only *HOXB13* (odds ratio [OR] = 4.63, 95% confidence interval [CI] = 3.26–6.59, $p = 1.4 \times 10^{-17}$) and *CHEK2* (OR = 2.06, 95% CI = 1.51–2.80, $p = 4.9 \times 10^{-6}$) reached genome-wide significance (Supplementary Fig. 1). Limiting to 151 DNA repair genes, which have been implicated in PCa risk [4,11], only *CHEK2* (see above) and *BRCA2* (OR = 2.15, 95% CI = 1.40–3.28, $p = 4.2 \times 10^{-4}$) were significantly associated with PCa risk after multiple testing adjustment (Supplementary Fig. 2). In individual exome-wide P/LP/D variant analyses, two significant associations were identified: known rs138213197 (G84E) in *HOXB13* (control carrier frequency = 0.31%, case carrier frequency = 1.29%, $p = 6.9 \times 10^{-18}$) and novel rs769540160 in *MYO3A* (control carrier frequency = 0.004%, case carrier frequency = 0.11%, $p = 1.1 \times 10^{-7}$; Supplementary Fig. 3). Although *MYO3A* was not genome-wide significant in gene-based tests, results were suggestive of carriers having 1.67-fold increased odds of PCa (95% CI = 1.06–2.65, $p = 0.027$). The carrier frequency of rs769540160 in 32 330 cancer-free European ancestry individuals in gnomAD was 0.009% [12], while it was four-fold more common in a whole-exome sequencing study of 5545 European ancestry men with aggressive and nonaggressive PCa, with a carrier frequency of 0.04% (carried by two men both of whom died due to PCa and had Gleason scores $\geq$8) [4]. Given the extreme rarity of this variant, additional large-scale PCa sequencing studies are necessary to further validate this novel association.

Combined rare and common variant analyses focused on carrier status of P/LP/D variants in known PCa risk genes (*HOXB13* and DNA repair genes *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *CHEK2*, *NBN*, and *MSH2*) [4,11,13] and our recently developed multiancestry PRS [5]. *HOXB13*, *BRCA2*, *ATM*, and *CHEK2* had sufficient numbers of P/LP/D carriers for analyses and were consequently the focus of our investigation. Analyses jointly evaluating the PRS and carrier status excluded *HOXB13* G84E and/or *CHEK2* 1100delC from the PRS when carrier status included either of these variants. Of the total 1576 carriers of P/LP/D alleles in these four genes, 19 men carried two P/LP/D alleles (including two cases) and the remaining 1557 men carried one P/LP/D allele (including 143 cases). As expected, these four genes showed strong associations with PCa risk, as did the multiancestry PRS, which had stronger effects than a previously developed European ancestry PRS [14] (Supplementary Tables 1 and 2). In aggregate, P/LP/D carriers had 2.52-fold increased odds of PCa (2.10–3.04, $p = 1.40 \times 10^{-22}$) and 4.73-fold increased odds of dying due to PCa (95% CI = 2.82–7.94, $p = 4.1 \times 10^{-9}$). Although we had insufficient clinical data to further evaluate aggressive or lethal disease (220 men died due to PCa, of whom 16 carried P/LP/D alleles in these genes), we previously reported that P/LP/D variants in *ATM* and *BRCA2* were more common in men with aggressive (and lethal) disease than in men with nonaggressive PCa [4]. Aggregate effects of P/LP/D variants in these genes did not differ significantly in men with and without a first-degree family history of PCa or in men $\leq$60 or >60 yr of age (Supplementary Tables 3 and 4). PRS effects also did not differ significantly by family history; however, the PRS had significantly larger effects in younger than in older men (Supplementary Tables 5 and 6), consistent with previous findings [5].

Relative to noncarriers in the average 40–60% PRS category, ORs ranged from 0.28 (95% CI = 0.22–0.36) to 4.34 (95% CI = 3.87–4.87) for noncarriers and from 1.06 (95% CI = 0.43–2.64) to 10.21 (95% CI = 6.53–15.96) for carriers in the lowest and highest PRS decile, respectively (Fig. 1A). The absolute risk of PCa by age 85 yr ranged from 2% to 31% for noncarriers and from 9% to 56% for carriers in the lowest and highest PRS decile, respectively (Fig. 1B). The absolute risk for carriers in the 90–100% PRS category (56%) was similar to the 55% absolute risk for men in the 99–100% PRS category (independent of carrier status) and two-fold higher than the 26% absolute risk for carriers (independent of PRS). The absolute risk for carriers in the 0–10% PRS category (9%) was similar to the 11% absolute risk for noncarriers (independent of PRS; Fig. 1C). Effects and absolute risks were slightly weaker when excluding *HOXB13* G84E from carrier status (Supplementary Fig. 4). Evaluation of the four genes separately revealed similar findings (Supplementary Fig. 5–8), with *HOXB13* G84E carriers having notably increased PCa risk compared with noncarriers across PRS quintiles (used instead of deciles, given the smaller numbers of carriers within individual genes). Across PRS quintiles, ORs for *HOXB13* G84E carriers ranged from 2.96 (95% CI = 1.19–7.34) to 10.10 (95% CI = 5.03–20.28; relative to *HOXB13* G84E noncarriers in the average 40–60% PRS category), while absolute risks for *HOXB13* G84E carriers ranged from 23% to 56% by age 85 yr (Supplementary Fig. 5). We observed a statistically significant interaction between the continuous PRS and carrier status for *HOXB13* ($p = 0.041$), but not for the other genes separately or in aggregate ($p \geq 0.14$; Supplementary Table 1).

Interestingly, among cases, *HOXB13* G84E was most common in the lowest PRS quintile (4.4%) and least common in the highest PRS quintile (0.5%), whereas control carrier frequencies across PRS quintiles were consistently 0.3% (Fig. 2A). Accordingly, the average PRS was higher in *HOXB13* G84E noncarriers than in carriers among cases ($p = 0.005$) and did not significantly differ by carrier status among controls ($p = 0.3$; Fig. 2B). The frequency of *CHEK2* P/LP/D carriers was also most common in cases in the lowest PRS quintile (2.3%) and least common in the highest PRS quintile (1.3%; Supplementary Fig. 9); however, PRS did not differ significantly by carrier status ($p = 0.3$; Supplementary

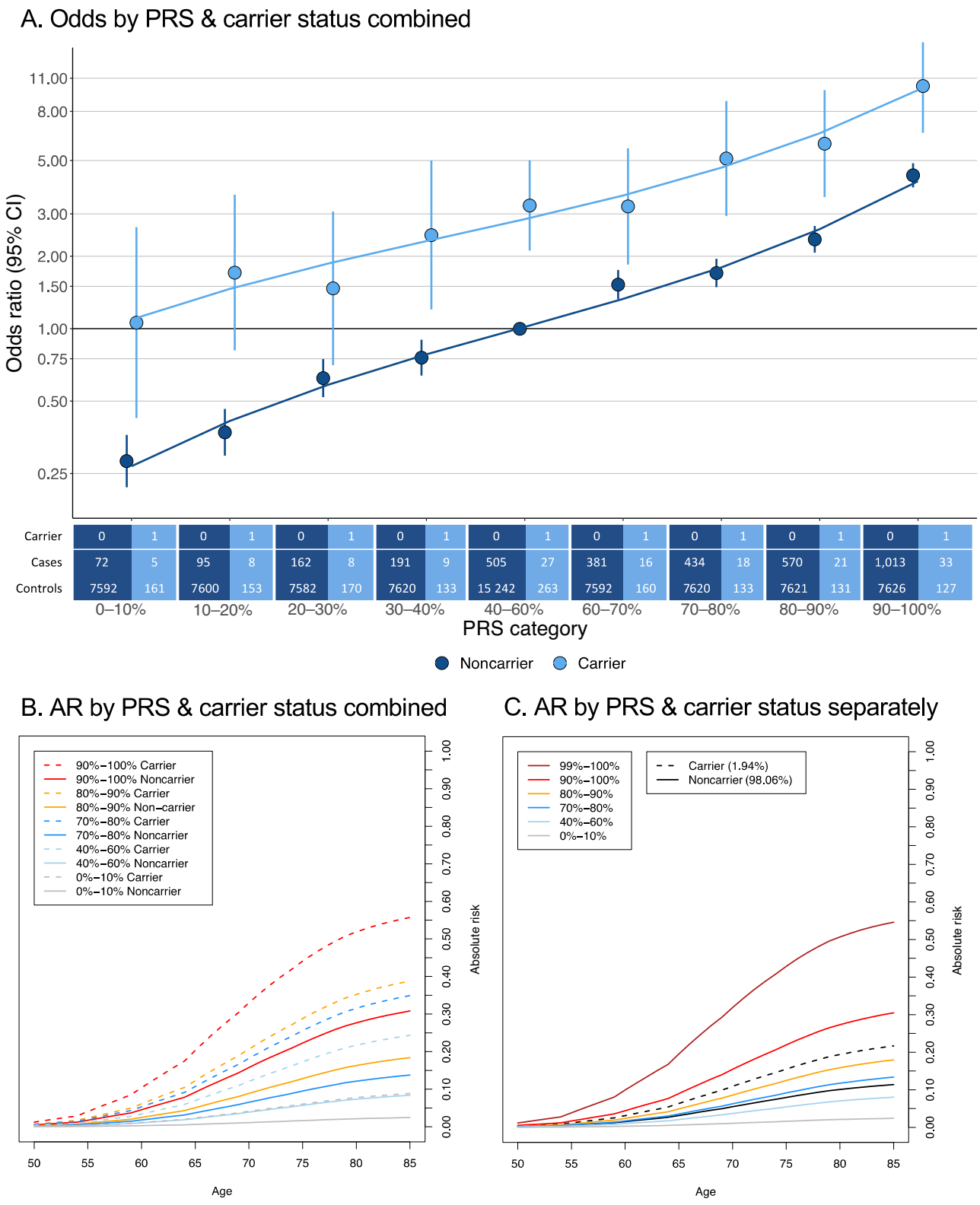

Fig. 1 – Aggregate effect of P/LP/D variants in *ATM*, *BRCA2*, *CHEK2*, and *HOXB13* and a polygenic risk score (PRS) on prostate cancer risk. (A) Odds of prostate cancer by PRS category and carrier status. ORs are calculated with respect to the referent noncarrier 40–60% PRS category. Sample sizes of carriers and noncarriers by case status and PRS category are indicated below the figure. In the 40–60% PRS category, 0.76% and 14.15% of total cases are carriers and noncarriers, respectively. ORs are plotted on a log scale. (B) Absolute risk (AR) of prostate cancer by age and the combination of carrier status and PRS category. The 40–60% PRS noncarrier line estimates baseline AR by age (8.4% lifetime AR). (C) AR of prostate cancer by age and carrier status (independent of PRS) and PRS category (independent of carrier status). The 40–60% PRS line (8.1% lifetime AR) and noncarrier line (11.3% lifetime AR) estimate baseline AR by age. CI = confidence interval; OR = odds ratio.

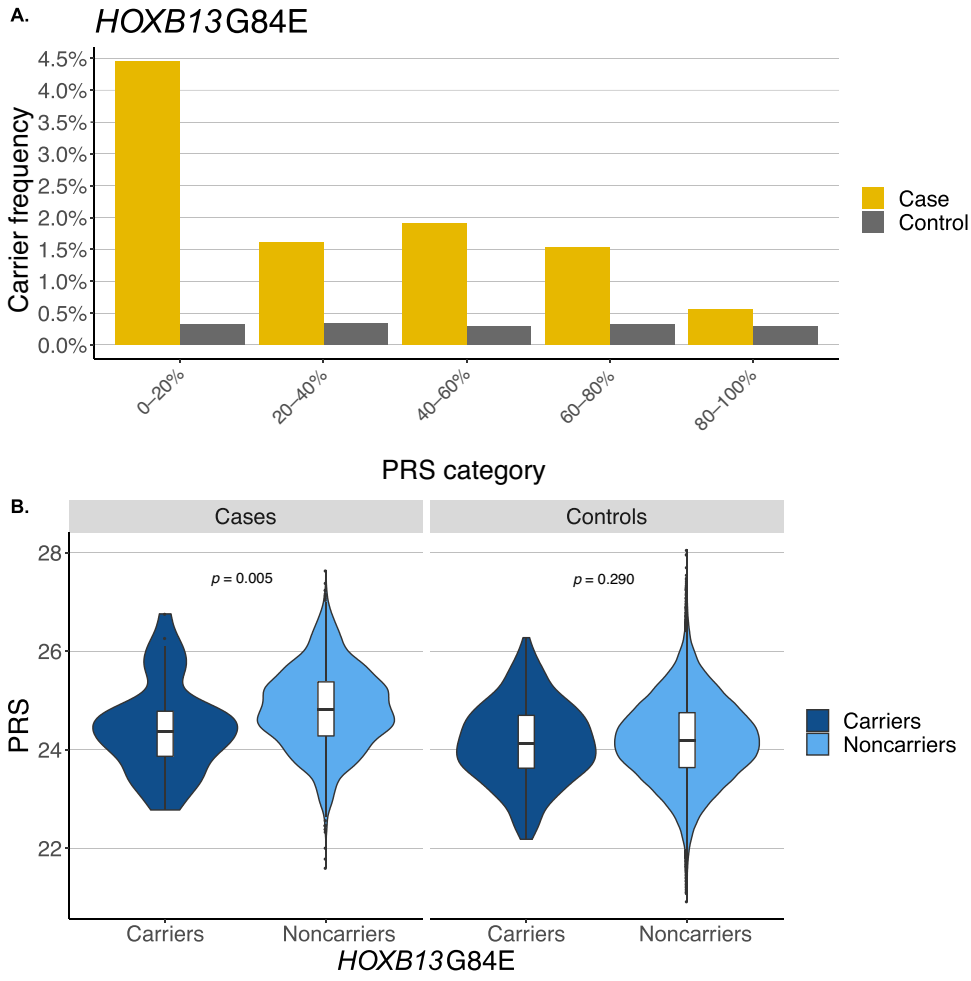

Fig. 2 – Polygenic risk score (PRS) and *HOXB13* G84E carrier status. (A) *HOXB13* G84E carrier frequency by PRS category and prostate cancer status. (B) PRS distribution by *HOXB13* G84E carrier status and prostate cancer status. PRS differences between carriers and noncarriers are calculated using a two-sided *t* test.

Fig. 10). The *HOXB13* G84E finding was validated using genome-wide association study (GWAS) data in an independent sample of 5197 cases and 115 796 controls in the UK Biobank, with cases having a carrier frequency of 3.2% in the lowest PRS quintile and 1.2% in the highest PRS quintile (Supplementary Fig. 11). Similar results were observed in the full UK Biobank sample (8765 cases and 193 322 controls; Supplementary Fig. 12). This finding suggests that *HOXB13* G84E may account for more PCa in men with low versus high PRS. While carrying rare or common risk variants could serve as independent pathways to PCa onset, our results suggest that carrying rare variants in these genes and having high PRS compound PCa risk.

Findings from this investigation suggest that PCa risk may vary depending on an individual's genetic profile of common risk variants, measured by PRS, and carrier status for rare P/LP/D variants in *HOXB13* and *BRCA2*, with novel evidence for variants in *CHEK2* and *ATM*. In particular, men in the top PRS decile had a higher absolute risk of PCa than carriers (31% vs 25%); however, considering the PRS and carrier status jointly, the absolute risk for noncarriers in the top PRS decile was 31%, while it increased to 56% for carriers in the top PRS decile. This is supported by previous findings of rare and common variants collectively improving discriminative ability of PCa risk models [15] and could have important clinical implications, such as informing decisions regarding PCa screening, with P/LP/D carriers and/or men with a high PRS potentially benefiting from earlier and more frequent screening. Further studies are underway and needed to evaluate the impact of such clinical implementations. Consistent with studies of other diseases [16], our findings also suggest that rare and common variants could independently lead to PCa onset, with low PRS cases being more likely to carry *HOXB13* G84E, for example. Whole-genome sequencing efforts could have improved the power to identify additional moderate- to high-penetrant rare PCa risk variants by prioritizing low PRS cases, as extreme sampling has been shown to improve the power to detect rare variants [17]. It will be important to extend this to clinical investigations to determine whether PRS in conjunction with carrier status for rare P/LP/D variants could better discern aggressive PCa, which we were unable to investigate in this study. Further, similar investigations in non-European ancestry men will be

critical, particularly in men of African ancestry, given the established genetic contribution to high PCa incidence rates in this population [5].

***Author contributions*:** Burcu F. Darst 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: Darst, Conti, Haiman.
Acquisition of data: Darst, Sheng, Haiman.
Analysis and interpretation of data: Eeles, Kote-Jarai, Conti, Haiman.
Drafting of the manuscript: Darst.
Critical revision of the manuscript for important intellectual content: Darst, Conti, Haiman.
Statistical analysis: Darst.
Obtaining funding: Darst.
Administrative, technical, or material support: Sheng.
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Appendix A. Supplementary data

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Platinum Priority – Editorial

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Incorporation of Polygenic Risk Score into Guidelines for Inherited Risk Assessment for Prostate Cancer

Jianfeng Xu [a,b], *William B. Isaacs* [c,*]

[a] *Program for Personalized Cancer Care, NorthShore University HealthSystem, Evanston, IL, USA;* [b] *Department of Surgery, NorthShore University HealthSystem, Evanston, IL, USA;* [c] *The Brady Urological Institute, The Johns Hopkins School of Medicine, Baltimore, MD, USA*

In this issue of *European Urology*, Darst and colleagues [1] report the combined effect of germline rare pathogenic mutations (RPMs) and a polygenic risk score (PRS) on prostate cancer (PCa) risk for more than 80 000 men from the UK Biobank (UKB). Several important findings were obtained, including (1) RPMs in *HOXB13* and *CHEK2* are predominantly found in men with low PRS, (2) RPMs in only four genes (*HOXB13*, *BRCA2*, *ATM*, and *CHEK2*) are significantly associated with PCa risk, and (3) the remarkable performance of RPMs and PRS in differentiating absolute PCa risk by age 85 yr for men in the general population, ranging from 2% for men with low risk (without RPMs and in the lowest PRS decile) to 56% for men with high risk (with RPMs and in the highest PRS decile). The first finding is novel (RPMs and PRS were previously thought to be independent) and requires confirmation in other studies. The last two findings confirm and expand previous reports [2–6] and thus are ripe for clinical translation. Here we summarize key findings regarding RPMs and PRS for urologists, discuss their potential clinical utility in PCa care and early detection, and identify translational research needed to underpin effective germline testing in the clinic.

1. Germline RPMs and PRS: complementary measures of inherited risk

Established PCa RPMs confer moderate PCa risk and are rare, regardless of family history (FH), at ~2% in the general population and ~5% in PCa patients [1,2,5]. By contrast, PCa PRS, calculated from hundreds of common, well-established, risk-associated single-nucleotide polymorphisms (SNPs), is more informative and can identify both low-risk and high-risk men in the general population [1,2,5].

It is of note that PRS is associated with risk of all forms of PCa, including lethal disease, but does not differentiate risk between indolent and aggressive PCa [1,2,5]. By contrast, RPMs in some genes (eg, *BRCA2* and *ATM*) are preferentially associated with high-grade and metastatic PCa [6]. Therefore, while both RPMs and PRS are informative for PCa risk assessment before PCa diagnosis, only RPMs are informative for predicting disease prognosis in men diagnosed with PCa.

2. Added value of RPMs and PRS to FH: observations from a population-based cohort

The frequency of established inherited risk factors and their respective PCa risk in the UKB are presented in Figure 1. Combined RPMs in *HOXB13, BRCA2*, *ATM*, and *CHEK2* are present in 1.7% of men in the cohort and are associated with an odds ratio (OR) of 3.00 for PCa (blue). By comparison, 2.6% of men have a high genetic risk score (GRS, an OR-weighted, population-standardized PRS) of three or more which is associated with a similar increase in risk (OR 4.48; green). Furthermore, 15% of men have moderately high GRS (between 1.5 and <3) with OR of 2.04 for PCa, similar to the increase in risk associated with FH (8.3% of men; OR 2.24; red). Using FH alone, ~8% of men will be identified as at high risk. Adding RPMs and GRS will identify ~2% and ~18% of men, respectively, as at high risk.

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* Corresponding author. The Brady Urological Institute, The Johns Hopkins School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA. Tel. +1 410 955 2518. E-mail address: wisaacs@jhmi.edu

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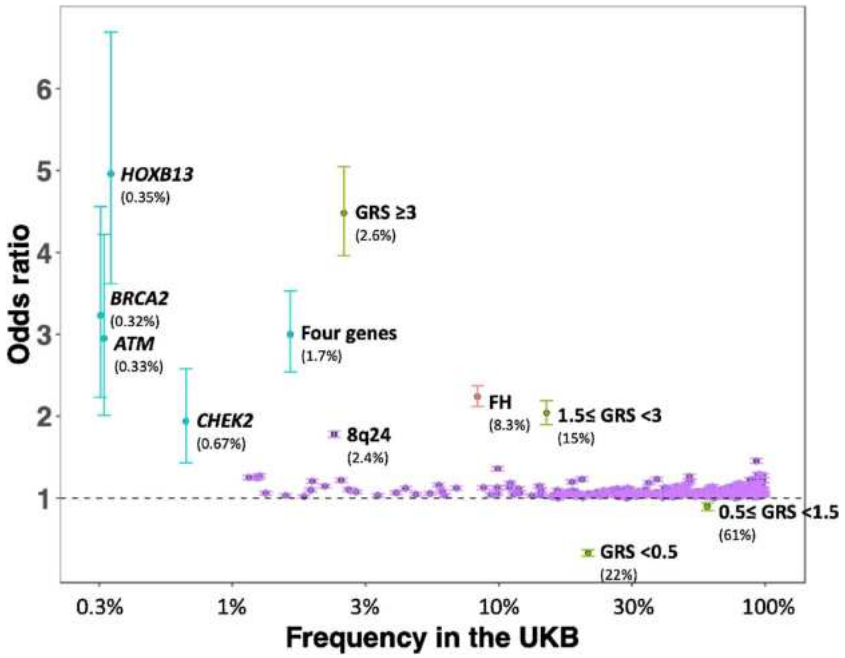

Fig. 1 – Observed prostate cancer risk and 95% confidence interval as a function of the frequency of established inherited risk measures based on our independent analysis of the UK Biobank (UKB). Blue denotes rare pathogenic mutations in genes that are significantly associated with prostate cancer risk (carrier frequency is shown). Red denotes family history (FH) of prostate cancer in father and/or brothers. Purple denotes 239 established risk-associated single-nucleotide polymorphisms (SNPs) identified from published genome-wide association studies (allele frequency is shown). Green denotes the genetic risk score (GRS) based on 239 risk-associated SNPs among Caucasians, categorized into four groups (GRS <0.5, 0.5–1.5, 1.5–3, and ≥3).

3. Clinical utility: developing personalized PCa screening strategies

The consistently demonstrated clinical validity of RPMs and PRS for identifying high-risk men and better quantifying PCa risk suggests their possible and necessary use in risk assessment for developing optimal personalized PCa screening strategies [1–5]. This proposition is not based on the flawless performance of both measurements but on the principle of comparative effectiveness. An important reminder is that the evidence and performance of these measurements for predicting PCa risk is stronger than FH, the predominant guideline-recommended measurement of inherited risk.

Current National Comprehensive Cancer Network (NCCN) guidelines for early detection of prostate cancer recommend inclusion questions on FH of cancer and family or personal history of high-risk germline mutations as part of the baseline evaluation of PCa risk for PCa screening [7]. The guidelines, which do not include PRS, have two major limitations: (1) FH eligibility would miss the vast majority of RPM carriers; and (2) without PRS, many high-risk men would be missed. We implore guideline committees to review data on RPMs and PRS and update their recommendations according to the available evidence. Incorporation of PRS and RPMs with FH in risk assessment will benefit not only men at high risk by recommending earlier and more frequent PCa screening but also men at low risk by recommending decreased or delayed PCa screening.

4. Clinical utility: predicting prostate biopsy outcomes

Another related clinical utility for RPMs and PRS is predicting PCa detection rates from prostate biopsies for men with elevated prostate-specific antigen. The utility of PRS in differentiating detection rates has been consistently demonstrated in all published studies, from retrospective analyses of clinical trials to clinical biopsy series [2]. For example, in the Prostate Cancer Prevention Trial, the detection rate from biopsy was 15% and 40% in men with low and high PRS values, respectively [8]. This discriminative performance might be explained by the presence of more positive and bilateral tumor cores in men with higher PRS (ie, genetic susceptibility for multifocal PCa) [9]. Incorporation of PRS and RPMs in decision-making for prostate biopsy together with other clinical variables addresses two key issues: improving the PCa detection rate while reducing unnecessary biopsies.

5. Translational research is urgently needed

Translational research is key to fulfilling the potential of previous discoveries. Several translational studies of RPMs and PRS are greatly needed. First, evidence-based research is needed to establish gene-PCa association for genes listed in the NCCN guidelines, a requirement for accurately annotating RPMs. Many of these genes are included because of their roles in cancer syndromes [7], but the association with PCa risk has yet to be established for most of them [2].

Second, efforts should be devoted to standardizing PRS methods for clinical implementation. Several methods have been proposed, including those based on hundreds of SNPs identified as significant in genome-wide association studies, thousands of risk-associated SNPs with less stringent significance levels, and millions of SNPs revealed via Bayesian genomic prediction methods. While these methods perform similarly [10], they differ considerably in clinical implementation. From the clinical use perspective, clinical-grade PRSs should be simple to interpret, well calibrated, and certified according to the Clinical Laboratory Improvement Amendments [10]. GRS is one PRS method that meets these considerations [2,10]. GRS is based on hundreds of established risk-associated SNPs. Its mean value in the population is always 1, regardless of how many SNPs are used. Furthermore, because it is calibrated and population-standardized, its value can be interpreted as relative risk in comparison to the general population.

Third, while the clinical validity of PCa PRS for men of European descent is well established, its validity for racial minorities needs further demonstration in large studies. This gap further exacerbates racial disparity in PCa care and should be urgently bridged. An important step in this process has recently been reported by Conti et al. [11].

Conflicts of interest: NorthShore University HealthSystem collaborates with Ambry Genetics and GoPath Laboratories to develop germline genetic tests for prostate cancer risk.

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Platinum Priority Brief Correspondence

Editorial by Stanley L. Liauw on pp. 147–148 of this issue

Patterns of Clinical Progression in Radiorecurrent High-risk Prostate Cancer

Rebecca G. Philipson [a,†], Tahmineh Romero [b,†], Jessica K. Wong [c], Bradley J. Stish [d], Robert T. Dess [e], Daniel E. Spratt [e], Avinash Pilar [f,g], Chandana Reddy [h], Trude B. Wedde [i], Wolfgang A. Lilleby [i], Ryan Fiano [j], Gregory S. Merrick [j], Richard G. Stock [k], D. Jeffrey Demanes [l], Brian J. Moran [m], Michelle Braccioforte [m], Phuoc T. Tran [n], Santiago Martin [o], Rafael Martinez-Monge [o], Daniel J. Krauss [p], Eyad I. Abu-Isa [e], Luca Valle [a], Natalie Chong [a], Thomas M. Pisansky [d], C. Richard Choo [d], Daniel Y. Song [n], Stephen Greco [n], Curtiland Deville [n], Todd McNutt [n], Theodore L. DeWeese [n], Ashley E. Ross [q], Jay P. Ciezki [h], Derya Tilki [r], R. Jeffrey Karnes [s], Eric A. Klein [t], Jeffrey J. Tosoian [u], Paul C. Boutros [v], Nicholas G. Nickols [a,w], Prashant Bhat [x], David Shabsovich [x], Jesus E. Juarez [x], Patrick A. Kupelian [a], Matthew B. Rettig [y,z], Alejandro Berlin [f], Jonathan D. Tward [aa], Brian J. Davis [d], Robert E. Reiter [v], Michael L. Steinberg [a], David Elashoff [b], Eric M. Horwitz [c], Rahul D. Tendulkar [h], Amar U. Kishan [a,v,]*

[a] *Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA, USA;* [b] *UCLA Division of General Internal Medicine and Health Services Research, Los Angeles, CA, USA;* [c] *Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA;* [d] *Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA;* [e] *Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA;* [f] *Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Canada;* [g] *Department of Radiation Oncology, University of Toronto, Toronto, Canada;* [h] *Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA;* [i] *Oslo University Hospital, Oslo, Norway;* [j] *Schiffler Cancer Center, Wheeling Hospital, Wheeling Jesuit University, Wheeling, WV, USA;* [k] *Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [l] *California Endocurietherapy Cancer Center, Oakland, CA, USA;* [m] *Chicago Prostate Cancer Center, Westmont, IL, USA;* [n] *Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [o] *Department of Radiation Oncology, Clínica Universidad de Navarra and Program in Solid Tumors, CIMA- University of Navarra, Pamplona, Spain;* [p] *Oakland University William Beaumont School of Medicine, Royal Oak, MI, USA;* [q] *Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;* [r] *Department of Urology and Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [s] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [t] *Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA;* [u] *Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [v] *Department of Urology, University of California Los Angeles, Los Angeles, CA, USA;* [w] *Department of Radiation Oncology, West Los Angeles Veterans Health Administration, Los Angeles, CA, USA;* [x] *David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA;* [y] *Department of Medical Oncology, University of California Los Angeles, Los Angeles, CA, USA;* [z] *Department of Medical Oncology, West Los Angeles Veterans Health Administration, Los Angeles, CA, USA;* [aa] *Department of Radiotherapy Oncology, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA*

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† These authors contributed equally to this work.
* Corresponding author. Department of Radiation Oncology, University of California Los Angeles, Los Angeles, 200 Medical Plaza, Los Angeles, CA 90095, USA. Tel. +1 310 825 9771; Fax: +1 310 794 9795.
E-mail address: aukishan@mednet.ucla.edu (A.U. Kishan).

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Abstract

The natural history of radiorecurrent high-risk prostate cancer (HRPCa) is not well-described. To better understand its clinical course, we evaluated rates of distant metastases (DM) and prostate cancer-specific mortality (PCSM) in a cohort of 978 men with radiorecurrent HRPCa who previously received either external beam radiation therapy (EBRT, n = 654, 67%) or EBRT + brachytherapy (EBRT + BT, n = 324, 33%) across 15 institutions from 1997 to 2015. In men who did not die, median follow-up after treatment was 8.9 yr and median follow-up after biochemical recurrence (BCR) was 3.7 yr. Local and systemic therapy salvage, respectively, were delivered to 21 and 390 men after EBRT, and eight and 103 men after EBRT + BT. Overall, 435 men developed DM, and 248 were detected within 1 yr of BCR. Measured from time of recurrence, 5-yr DM rates were 50% and 34% after EBRT and EBRT + BT, respectively. Measured from BCR, 5-yr PCSM rates were 27% and 29%, respectively. Interval to BCR was independently associated with DM ($p < 0.001$) and PCSM ($p < 0.001$). These data suggest that radiorecurrent HRPCa has an aggressive natural history and that DM is clinically evident early after BCR. These findings underscore the importance of further investigations into upfront risk assessment and prompt systemic evaluation upon recurrence in HRPCa.
Patient summary: High-risk prostate cancer that recurs after radiation therapy is an aggressive disease entity and spreads to other parts of the body (metastases). Some 60% of metastases occur within 1 yr. Approximately 30% of these patients die from their prostate cancer.

More than 50% of men with high-risk prostate cancer (HRPCa)—defined as the presence of Gleason grade group 4–5 disease, clinical T stage 3–4, or prostate-specific antigen (PSA) >20 ng/ml—will develop biochemical recurrence (BCR) during extended follow-up [1]. These recurrences, termed "radiorecurrence" in the context of BCR after radiotherapy (RT), are currently defined as a rise in PSA of ≥2 ng/ml above the post-RT nadir [2] and could represent local, regional, or distant disease. Management options include observation, androgen deprivation therapy (ADT), metastasis-directed therapy, and local salvage therapies [3,4], but the choice of treatment is obfuscated by a lack of prospective studies and a limited understanding of the natural history of radiorecurrent HRPCa. The purpose of this study was to evaluate clinical outcomes after BCR among patients who received definitive external beam RT (EBRT) or EBRT with a brachytherapy boost (EBRT + BT) for HRPCa.

The study population consisted of 978 men who developed BCR (defined as PSA nadir + ≥2 ng/ml [2]) after receiving EBRT (n = 654, 67%) or EBRT + BT (n = 324, 33%) for HRPCa across 15 institutions from 1997 to 2015 (Supplementary Table 1). Follow-up times from completion of RT and from the date of BCR were summarized using the median and interquartile range (IQR) for men who did not die, and separately for men who did not develop distant metastasis (DM). The primary outcomes were DM and prostate cancer–specific mortality (PCSM), measured from the date of BCR. To better understand whether certain pretreatment and post-treatment characteristics might be associated with the development of metastases or mortality events after recurrence, multivariable Cox proportional-hazard models were used to evaluate the effects of the following prespecified covariates: age, Gleason grade group, ln(initial PSA [iPSA]), clinical T stage, and interval to BCR (calculated from the RT completion date to the date of BCR) on DM and PCSM. Models were assessed for the proportionality hazard assumption based on weighted residuals and observational tools [5]. Multivariable Cox proportional-hazard models adjusted for the same above-mentioned covariates were used to compare differences in time to systemic salvage therapy (initiation of new systemic therapies—including ADT and nonhormonal therapies—for radiorecurrence). Fine-Gray competing-risk regression models were also used to determine covariate-adjusted subdistribution hazard ratios (sHRs; adjusted for age at treatment, ln[iPSA], Gleason grade group, clinical T stage, interval to BCR, and treatment arm) for DM and PCSM after BCR. Death was the competing risk for DM and other-cause mortality was the competing risk for PCSM. Fisher's exact test and a Wilcoxon rank-sum test were used to evaluate differences in categorical and continuous variables, respectively, between EBRT and EBRT + BT. Tests of heterogeneity for all covariates between the treatment groups for both DM and PCSM were assessed using multivariable Cox regression models that included interaction terms between treatment arm and other predictors. Kaplan-Meier methods were used to generate survival curves.

For men who did not die, median follow-up was 8.9 yr from RT completion and 3.7 yr from BCR. Clinicopathologic features at diagnosis are shown in Supplementary Table 2. Details of the treatments received are shown in Supplementary Table 3. Most men (90%) received neoadjuvant/concurrent ADT (90% with EBRT, median duration 23 mo; 91% with EBRT + BT, median duration 8 mo). ADT duration was significantly longer in the EBRT group ($p <$ 0.001). Local salvage was performed in 21 patients after EBRT and in eight patients after EBRT + BT. Systemic salvage was used in 390 men after EBRT and 103 men after EBRT + BT; there was no significant difference between time to initiation of systemic salvage between EBRT and

EBRT + BT (adjusted HR 1.01, 95% confidence interval [CI] 1.00–1.03; $p = 0.14$).

Kaplan-Meier curves for DM-free survival (DMFS) and prostate cancer–specific survival (PCSS) are presented in Figure 1. Measured from time of BCR, the 5-yr cumulative DM incidence rate was 50% among men treated with EBRT and 34% among men treated with EBRT + BT. Development of BCR within 3 yr of RT occurred in 378 men (261 after EBRT and 117 after EBRT + BT). A total of 330 men developed DM after EBRT and 105 developed DM after EBRT + BT. Among 435 men who developed distant failure, DM occurred within 1 yr of BCR in 189 EBRT patients and 59 EBRT + BT patients. Measured from BCR, the 5-yr cumulative PCSM incidence was 27% overall, with incidences of 27% after EBRT and 29% after EBRT + BT.

Several significant interaction terms between treatment arm and predictors in Cox regression models for time to PCSM and DM were identified, suggesting heterogeneity of covariates across treatment arms (Supplementary Table 4). Therefore, Cox models for DM and PCSM are presented for each treatment arm (EBRT and EBRT + BT) separately in Table 1, with competing-risk regression models in Supplementary Table 5. On stratified multivariable Cox regression for both EBRT and EBRT + BT, interval to BCR was a predictor for DM (EBRT: HR 0.84, 95% CI 0.78–0.89; $p < 0.001$; EBRT + BT: HR 0.87, 95% CI 0.77–0.99; $p = 0.03$) and PCSM (EBRT: HR 0.72, 95% CI 0.63–0.81; $p < 0.001$; EBRT + BT: HR 0.81, 95% CI 0.69–0.94; $p = 0.008$; Table 1).

This study represents the largest series of clinical outcomes for men with radiorecurrent HRPCa receiving definitive therapy in the modern era. A remarkably high number of DMs were diagnosed within 1 yr of BCR. Further highlighting the aggressive natural history, 5-yr estimates of PCSM were nearly 30%. The only consistent predictor of DM and PCSM across both EBRT and EBRT + BT, as well as in the entire cohort, was interval to BCR, with longer interval associated with lower risk of DM and PCSM. This finding is consistent with prior reports for all-risk prostate cancer [1,6].

Early DMs after BCR may be manifestations of occult micrometastatic disease present at the time of RT that ultimately progressed after cessation of ADT (or with castrate resistance). A proportion of these DMs may also simply reflect rapid progression from local recurrence to distant failure. The latter may also explain the separation of the DMFS curves (and rates) beyond the 1-yr mark: it is possible that greater initial local tumor eradication by the BT boost [7] may reduce these "late waves" of DMs [8], which would explain, at least in part, the overall lower DM rate observed after EBRT + BT compared to EBRT. As advanced imaging techniques, such as prostate-specific membrane antigen positron emission tomography/comput-

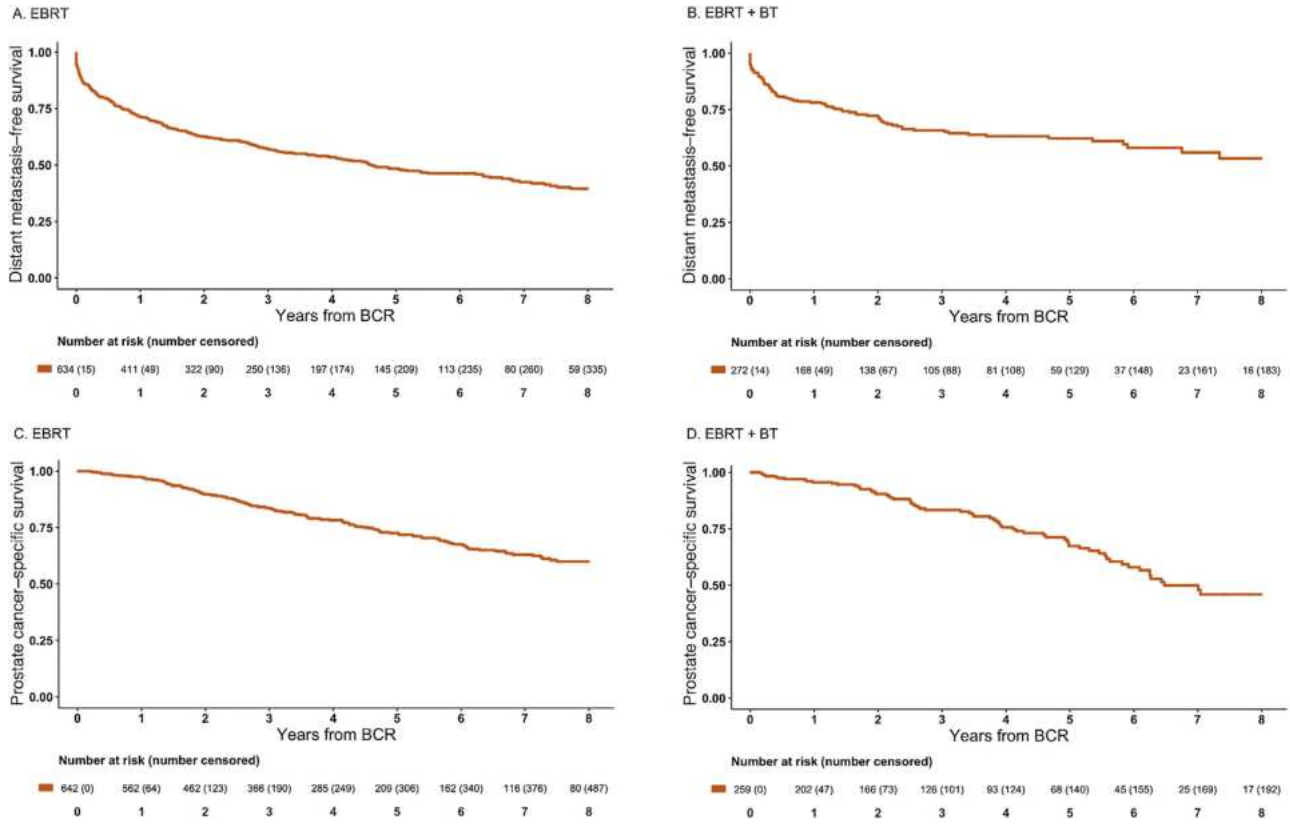

Fig. 1 – Kaplan-Meier curves for (A,B) distant metastasis–free survival and (C,D) prostate cancer–specific survival following biochemical recurrence (BCR) in men with high-risk prostate cancer treated initially with external beam radiotherapy (EBRT) or external beam radiotherapy plus brachytherapy boost (EBRT + BT). (A) Distant metastasis–free survival following BCR after EBRT. (B) Distant metastasis–free survival following BCR after EBRT + BT. (C) Prostate cancer–specific survival following BCR after EBRT. (D) Prostate cancer–specific survival following BCR after EBRT + BT.

Table 1 – Multivariable Cox proportional-hazard model for prediction of distant metastasis and prostate cancer–specific mortality stratified by treatment for men with radiorecurrent high-risk prostate cancer

	Distant metastasis		Prostate cancer–specific mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
External beam radiation therapy				
Interval to biochemical failure [a]	0.84 (0.78–0.89)	<0.001	0.72 (0.63–0.81)	<0.001
Age at treatment (per 5-yr increment)	1.01 (0.93–1.09)	0.8	1.04 (0.94–1.16)	0.4
ln(iPSA)	0.88 (0.77–1.01)	0.064	0.85 (0.7–1.03)	0.095
Gleason grade group (reference: GG1) [b]				
GG 2	1.32 (0.62–2.81)	0.5	5.14 (0.64–41.22)	0.12
GG 3	2.03 (0.95–4.30)	0.066	9.16 (1.17–71.85)	0.035
GG 4	1.89 (0.96–3.69)	0.064	7.94 (1.06–59.14)	0.043
GG 5	2.35 (1.19–4.65)	0.014	17.24 (2.33–127.45)	0.005
Clinical T stage (reference: cT1c) [c]				
cT2a	1.50 (0.95–2.36)	0.083	1.08 (0.56–2.05)	0.8
cT2b	1.00 (0.64–1.57)	>0.9	0.91 (0.46–1.8)	0.8
cT2c	0.91 (0.56–1.48)	0.7	0.77 (0.37–1.61)	0.5
cT3a	1.33 (0.88–2.03)	0.18	1.10 (0.58–2.08)	0.8
cT3b	1.22 (0.77–1.94)	0.4	1.19 (0.62–2.28)	0.6
cT4	2.27 (1.22–4.23)	0.010	1.87 (0.84–4.13)	0.12
External beam radiation therapy + BT				
Interval to biochemical failure [a]	0.87 (0.77–0.99)	0.031	0.81 (0.69–0.94)	0.008
Age at treatment (per 5-yr increment)	1.00 (0.85–1.18)	>0.9	0.96 (0.79–1.17)	0.7
ln(iPSA)	0.83 (0.60–1.15)	0.3	0.78 (0.53–1.15)	0.2
Gleason grade group (reference: GG1) [b]				
GG 2	0.29 (0.05–1.78)	0.18	0.46 (0.08–2.64)	0.4
GG 3	–	––	–	–
GG 4	0.28 (0.09–0.91)	0.035	0.17 (0.04–0.73)	0.017
GG 5	0.33 (0.1–1.05)	0.060	0.54 (0.14–2.11)	0.4
Clinical T stage (reference: cT1c) [c]				
cT2a	0.35 (0.12–1.01)	0.053	0.24 (0.06–1)	0.050
cT2b	0.73 (0.33–1.61)	0.4	0.69 (0.28–1.68)	0.4
cT2c	0.63 (0.24–1.65)	0.3	0.88 (0.32–2.47)	0.8
cT3a	0.86 (0.4–1.82)	0.7	1.37 (0.64–2.96)	0.4
cT3b	0.26 (0.07–0.97)	0.045	0.4 (0.1–1.68)	0.2
cT4	–	––	–	–

PC = prostate cancer; BT = brachytherapy boost; HR = hazard ratio; CI = confidence interval; GG = grade group; ln(iPSA) = natural log of initial prostate-specific antigen.
[a] Per 1-yr increment.
[b] Per grade group increment.
[c] Per cT stage increment.

ed tomography, are further integrated into initial staging, identification of occult DM in high-risk populations may enhance upfront patient selection and treatment decision-making [9,10].

There are several limitations to this study. There are likely to be significant selection biases that impacted the choice of treatment with EBRT or EBRT + BT, such as performance status and comorbidities; these factors may have implications for a patient's life expectancy, ability to tolerate upfront systemic therapies, and ability to undergo salvage therapies. In effect, the rates of DM and PCSM presented—and any differences observed between treatments—are not solely reflective of outcomes after each treatment but may also reflect potential comorbidity confounders. Unfortunately, medical comorbidity data were not available. In addition, owing to the nature of multivariable analyses, the aggregate clinical picture of where each patient fell on the high-risk spectrum was not included in these models or outcomes, so treatment selection bias for very high-risk patients could also have influenced the predictive model results. Furthermore, details regarding diagnostic evaluation at the time of BCR, such as timing and use of imaging studies to detect local or distant recurrence, or biopsies of the prostate and/or potential metastatic sites, were not available. Thus, we cannot know the distribution of biochemical failures that were attributable to local recurrence, DM, or a combination of the two. This also precludes our ability to report the percentage of patients who received local salvage among those who were appropriate candidates. Further study is needed to better understand which men with radiorecurrent HRPCa might benefit from local salvage therapy.

Overall, our findings indicate that recurrence after RT for HRPCa follows an aggressive clinical course, as many these patients develop early metastases and may harbor micrometastatic disease. The markedly high rate of PCSM probably reflects that HRPCa that recurs after both ADT and local definitive treatment is biologically aggressive disease. Further studies are warranted to better evaluate whether advanced imaging and risk stratification tools can change the natural history after recurrence, and

potentially even improve clinical outcomes by informing the initial treatment strategy for high-risk patients.

Author contributions: Amar U. Kishan 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: Kishan, Philipson, Romero.
Acquisition of data: Kishan, Philipson, Wong, Stock, Demanes, Nickols, Shabsovich, Moran, Braccioforte, Tendulkar, Martin, Martinez-Monge, Horwitz, Tran, Ciezki, Spratt, Dess, Pilar, Stish, Wedde, Lilleby, Fiano, Merrick, Krauss, Abu-Isa, Deville, McNutt, Davis, Tward.
Analysis and interpretation of data: Romero, Kishan, Philipson.
Drafting of the manuscript: Philipson, Kishan, Romero.
Critical revision of the manuscript for important intellectual content: Boutros, Stock, Rettig, Kupelian, Romero, Kishan, Philipson, Nickols, Steinberg, Spratt, Juarez, Bhat, Berlin, Horwitz, Elashoff, DeWeese, Ross, Tilki, Karnes, Valle, Chong, Pisansky, Choo, Song, Greco, Reddy, Reiter, Tosoian.
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Other: None.

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Data sharing statement: Owing to multi-institutional data sharing policies and restrictions, research data are not available for sharing at this time.

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.2021.04.035.

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Platinum Priority – Editorial

Referring to the article published on pp. 142–146 of this issue

High-risk Prostate Cancer Treated with Radiation Therapy: Opportunities to Reduce Cancer Mortality after Biochemical Failure

Stanley L. Liauw *

Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL, USA

A primary goal of the oncologist is to effectively treat cancer that would otherwise cause morbidity or mortality, while preserving pretreatment quality of life to the fullest extent possible. Identifying the perfectly suited treatment recommendation for a man with prostate cancer can be a challenge given the heterogeneity of prostate cancer risk and a competing risk of noncancer mortality that can supersede the natural history of cancer progression. To that end, local therapy for prostate cancer is generally recommended only when life expectancy exceeds 20, 10, and 5 yr for prostate cancer with National Comprehensive Cancer Network (NCCN) very low, low/intermediate, or high/very high risk, respectively. Decisions regarding therapy for men who experience biochemical failure can be more complicated. In a man with rising prostate-specific antigen (PSA) after radical prostatectomy, salvage radiation therapy (RT) is commonly considered if life expectancy exceeds the 8–10 yr during which distant metastasis could otherwise occur [1] owing to its treatment efficacy and reasonable risks for quality of life [2]. In a man with a rising PSA after RT, the source of the PSA recurrence and time course to progression are less well defined, and treatment efficacy and associated risks may also be less favorable. In addition, because men who receive RT are often older or have greater medical comorbidity, they are also more likely to die from competing risks, raising the question of whether aggressive treatment is necessary.

In this issue of *European Urology*, Philipson et al [3] present welcome data on the outcomes for men who experience biochemical recurrence after RT. In this retrospective study, 938 men were treated for high-risk prostate cancer with external beam RT with or without brachytherapy boost. At median follow-up of 3.7 yr after PSA failure, 435 men (46%) developed distant metastasis, with the majority of metastases detected within the first year, presumably coinciding with recovery of testosterone after androgen deprivation therapy (ADT). The 5-yr rates of distant metastasis and cancer mortality were 50% and 27%, respectively. A cumulative incidence analysis to account for competing risks of mortality was not offered, but given the outcomes and follow-up duration, death from other causes seems unlikely to interfere with the force of disease progression and thereby compromise the value of cancer treatment.

The benchmark numbers in this report, which are consistent with two other large series [4,5], indicate that the average patient with biochemical failure after RT for high-risk cancer is at significant risk of clinical progression and death, especially if life expectancy exceeds 5 yr. Prompt diagnostic workup and consideration of salvage therapy are warranted for the majority of such men, save perhaps for those with the longest interval to recurrence and greatest medical comorbidity. Therapies for which early intervention could result in a more favorable outcome are justified, although the success and optimal prioritization of candidate therapies could be debated. Salvage local therapy can offer a PSA response for some men, as a significant proportion of men with failure after RT can have locally persistent disease. However, the long-term value of further local therapy may be limited by the risk of occult metastatic disease, as well as the potential for higher toxicity. Oligometastasis-directed therapies guided by novel positron emission tomography

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* Department of Radiation and Cellular Oncology, University of Chicago, 5758 S. Maryland Avenue, Chicago, IL 60637, USA. Tel. +1 773 702 6780; Fax: +1 773 834 7183. E-mail address: sliauw@radonc.uchicago.edu.

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(PET) radiotracers present hope for delaying the time to hormonal therapy, if not improve metastasis or survival, but more studies are necessary before considering this a standard of care [6]. Early salvage ADT, which may be the therapy most commonly offered, may delay castrate resistance and improve survival over delayed therapy [7], but compromises immediate quality of life and does not offer a durable PSA response after discontinuation.

This study highlights a few clinical practice points and areas of need for future research in the treatment of high-risk prostate cancer with RT, which can be categorized into three time points with respect to primary treatment. First, the finding of early metastatic progression in a substantial proportion of men underscores the value of appropriate staging and risk classification at diagnosis; the best opportunity to reduce mortality is likely to come from optimizing initial therapy. Strides have been made in both areas, and these recent advances may improve outcomes. For example, prostate-specific membrane antigen (PSMA)-based PET can identify patients with occult metastatic disease who might benefit from alternative therapies. In the proPSMA randomized trial of men with high-risk disease eligible for prostatectomy or RT, PET with ^{68}Ga-labeled PSMA ligand demonstrated superior diagnostic accuracy compared to conventional imaging, and resulted in a conversion to palliative therapy in 14% of men. Regarding risk classification, NRG Oncology PREDICT-RT is an exciting study that will evaluate use of a genomic test to adjust the intensity of ADT in men who receive RT. Randomized trials of RT show improved local and distant control with the addition of long-term ADT. The hope is that more potent hormonal agents can augment this effect, and thus far studies with abiraterone support this hypothesis in locally advanced disease [8] or NCCN unfavorable intermediate- or high-risk disease [9]. Second, following completion of RT, early markers of disease response to guide adjuvant therapy would be helpful. Candidates for response assessment in this relatively understudied area include post-RT magnetic resonance imaging or PET, the use of PSA kinetics or other blood biomarkers, and prostate biopsy. The length of adjuvant ADT after RT is typically decided at presentation, but committing to 18–36 mo without adapting to disease response potentially misses a chance to further personalize therapy. Third, at the time of biochemical recurrence, accurate restaging, such as with a PET radiotracer, would ideally guide selection of the most appropriate therapy. While the therapeutic ratio of salvage treatment is often not as favorable as that of initial therapy, progress has been made in defining efficacy and safety [10], making the once taboo choice of re-irradiation a legitimate option today. Further studies on the ideal timing, selection, and efficacy of salvage therapy are necessary, and at least until there are higher levels of evidence available, multidisciplinary discussion should be a mainstay in decision-making.

In summary, Philipson et al [3] are congratulated for their contribution. The study provides us with useful practical knowledge towards our goal as oncologists to offer treatment when clinically necessary, and these outcomes serve as a foundation for further improvement.

Conflicts of interest: The author has nothing to disclose.

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Platinum Priority – Bladder Cancer

Editorial by Gottfrid Sjödahl, Fredrik Liedberg, Mattias Höglund and Pontus Eriksson on pp. 160–161 of this issue

Molecular Characterization of Residual Bladder Cancer after Neoadjuvant Pembrolizumab

Andrea Necchi[a,b,**], *Joep J. de Jong*[c], *Daniele Raggi*[b], *Alberto Briganti*[a,d], *Laura Marandino*[e], *Andrea Gallina*[d], *Marco Bandini*[d], *Bashar Dabbas*[f], *Elai Davicioni*[f], *Umberto Capitanio*[d], *Francesco Montorsi*[a,d], *Roland Seiler*[g], *Jonathan L. Wright*[h], *Yair Lotan*[i], *Peter C. Black*[j], *Ewan A. Gibb*[k,*]

[a] *Vita-Salute San Raffaele University, Milan, Italy;* [b] *Department of Medical Oncology, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy;* [c] *Department of Urology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands;* [d] *Department of Urology, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy;* [e] *Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland;* [f] *Decipher Biosciences Inc., San Diego, CA, USA;* [g] *Department of Urology, University Hospital Bern, Bern, Switzerland;* [h] *Department of Urology, University of Washington, Seattle, WA, USA;* [i] *Department of Urology, UT Southwestern Medical Center, Dallas, TX;* [j] *Department of Urologic Sciences, University of BC, Vancouver, BC, Canada;* [k] *Decipher Biosciences Inc., Vancouver, British Columbia, Canada*

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Abstract

Background: In patients with muscle-invasive urothelial bladder cancer (MIBC), molecular alterations in immunotherapy-resistant tumors found at radical cystectomy (RC) remain largely unstudied.
Objective: To investigate the biology of pembrolizumab-resistant tumors in comparison to an RC cohort treated without any systemic therapy and a cohort of neoadjuvant chemotherapy (NAC)-treated tumors.
Design, setting, and participants: Transcriptome-wide expression profiling was performed on 26 RC samples from patients with ypT2–4 disease after pembrolizumab treatment, of which 22 had matched pretherapy samples. Unsupervised consensus clustering (CC) was performed to compare 26 post-pembrolizumab samples with 94 RC samples without neoadjuvant treatment and 21 samples collected from the former tumor bed of NAC-treated patients (scar tissue). Clusters were investigated for their biological and clinical characteristics and were compared to a cohort of post-NAC tumors ($n = 133$).
Outcome measurements and statistical analysis: Patient and tumor characteristics were compared between subgroups using χ^2 tests and two-sided Wilcoxon rank-sum tests. The primary endpoint was recurrence-free survival.
Results and limitations: Molecular subtyping of pre- and post-pembrolizumab samples revealed significant differences: only 36% of samples had a concordant subtype according to the consensus classifier. Unsupervised CC revealed three distinct post-pembrolizumab clusters (basal, luminal, and scar-like). A scar-like subtype was present in 50% of the post-pembrolizumab cases ($n = 13$) and expressed genes associated with wound

* Corresponding author. Decipher Biosciences Inc., 1152 Mainland Street #430, Vancouver, BC V6B 4X2, Canada.
E-mail addresses: ewan.gibb@decipherbio.com (E.A. Gibb).
** Corresponding author. Department of Medical Oncology, IRCCS San Raffaele Hospital and Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 02 26435789.
E-mail address: necchi.andrea@hsr.it (A. Necchi).

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healing/scarring. This subtype had higher luminal marker expression in the post-pembrolizumab setting compared to CC scar-like tumors from the other cohorts. Patients with the scar-like subtype showed favorable prognosis after systemic therapy, but not in the RC-only setting. The small numbers in each subgroup represents the major study limitation.
Conclusions: This study expands our understanding of the biology of pembrolizumab-resistant MIBC and provides a framework for defining molecular subtypes after treatment. The results further support the hypothesis that luminal-type tumors may be resistant to immunotherapy or that this treatment may select for, or induce, a luminal phenotype.
Patient summary: We carried out genetic analysis for bladder cancer tumors from patients who had received an immunotherapy agent called pembrolizumab and compared them to tumors treated with standard chemotherapy or just bladder removal. We found differences in gene expression between the treatment types and between tumor tissue from the same patient before and after treatment. These results may be helpful in personalizing therapy strategies for patients with bladder cancer.

1. Introduction

Muscle-invasive bladder cancer (MIBC) is an aggressive disease that demonstrates moderate response rates to standard cisplatin-based neoadjuvant chemotherapy (NAC) with a modest improvement in overall survival [1]. The approximately 50% of patients who are cisplatin-ineligible are treated with immediate radical cystectomy (RC) or are enrolled in clinical trials [2,3]. A number of novel therapies are being evaluated in the perioperative setting, of which immune checkpoint inhibition is the most advanced in clinical development. Response rates to immune checkpoint inhibitors are similar to those for platinum-based chemotherapy [4,5], which means that the majority of patients appear to gain no benefit. There is therefore a need for better patient selection and a better understanding of mechanisms of resistance to immunotherapy.

Molecular subtyping has advanced our understanding of MIBC, showing emerging utility in predicting response to treatment with both cisplatin-based NAC and checkpoint inhibitors [6–10]. Furthermore, more is known about the molecular alterations induced by NAC. For example, in NAC-treated patients, divergent response to NAC is reflected by a shift in the biological and clinical behavior of MIBC, impacting the molecular subtype of the tumor [10,11]. It has also been shown that NAC induces a epithelial-mesenchymal transition (EMT) phenotype [12], which is also observed with wound healing or in scar-like/p53-like tumors [10,11]. Chemotherapy also alters the mutational landscape/clonal evolution of a patient's tumor over time [13].

Conversely, very little is known regarding the molecular alterations induced by immune checkpoint inhibitors in treatment-resistant tumors. In the phase 2 ABACUS study, which tested the activity of preoperative atezolizumab before RC, a number of dynamic molecular changes were noted in pathological specimens after therapy [4]. In half of the patients with stable disease after treatment with atezolizumab, the tumor was categorized as an inflamed molecular subtype (ie, infiltrated subtype, 2012 Lund [14]) [4]. Whether this reflected enrichment for a particular tumor subtype or a response to treatment pressure is unknown.

In this study, we assembled a cohort of residual bladder tumors after pembrolizumab treatment (PURE-01) and compared these to a cohort of post-chemotherapy residual tumors and an RC cohort with no systemic neoadjuvant treatment.

2. Patients and methods

2.1. Patient cohorts

We analyzed RC tissue from three cohorts of patients with MIBC (Table 1): (1) UTSW: 94 patients from the University of Texas Southwestern Medical Center who underwent RC without neoadjuvant therapy [15]; (2) PURE-01: 26 patients with residual MIBC after neoadjuvant pembrolizumab; and (3) NAC: 133 patients with residual invasive (≥ypT1) tumor after cisplatin-based NAC [11]. For the PURE-01 cohort, we also analyzed matched transurethral resection of bladder tumor (TURBT) specimens from 22 patients, as previously reported [6]. We also analyzed 21 non-neoplastic samples from the former tumor bed of RC specimens with a complete pathologic response (ypT0N0) following NAC [11]. Data for the UTSW and NAC cohorts and scar tissue are available in the Gene Expression Omnibus repository under accession codes GSE128702 and GSE124305, respectively. The PURE-01 data are available on request for noncommercial research purposes. Requests can be made via partner@decipherbio.com.

2.2. Tissue sampling and gene expression profiling

Specimen collection and sample processing were conducted as previously described [6,11,15], using Decipher (Decipher Biosciences Laboratory, San Diego, CA, USA), a clinical-grade whole-transcriptome assay to measure gene expression. A detailed description of the methods is provided in the Supplementary material.

2.3. Unsupervised consensus clustering

Details of the unsupervised clustering analysis (R package *ConsensusClusterPlus*; R Foundation for Statistical Computing, Vienna, Austria) are provided in Supplementary material. Two clustering solutions were generated, one for UTSW ($n = 94$) and scar tissues ($n = 21$), and one for UTSW ($n = 94$), PURE-01 ($n = 26$), and scar tissues ($n = 21$).

Table 1 – Clinical characteristics of the UTSW, PURE-01, and NAC cohorts

Variable	UTSW	PURE-01	NAC
Patients (*n*)	94	26	133
Median age, yr (IQR)	70 (63–77)	68 (62–74)	63 (56–69)
Female gender, *n* (%)	16 (17)	3 (11.5)	36 (27.1)
Smoking status, *n* (%)			
Nonsmoker	17	8 (30.8)	0
Current smoker	0	4 (15.4)	0
Former smoker	0	14 (53.8)	0
Unavailable	77	0	133 (100)
Clinical T stage, *n* (%)			
cTis/Ta	4 (4.3)	0	0
cT1	10 (10.6)	0	0
cT2	66 (70.2)	7 (26.9)	60 (45.1)
cT3	9 (9.6)	15 (57.7)	53 (39.9)
cT4	4 (4.3)	4 (15.4)	20 (15)
cTx	1 (1.1)	0	0
Pathological T stage, *n* (%)			
pTa/pTis	1 (1.1)	1 (3.9)	0
pT1	0	0	10 (7.5)
pT2	33 (35.1)	6 (23.1)	38 (28.6)
pT3	42 (44.7)	17 (65.4)	62 (46.6)
pT4	15 (16)	2 (7.7)	23 (17.3)
Unavailable	0	0	0
Median lymph nodes removed, *n* (IQR)	21 (16–30)	27 (20–33)	20 (14–29)
Pathologically positive lymph nodes, *n* (%)			
No	62 (66)	11 (42.3)	69 (51.9)
Yes	31 (33)	15 (57.7)	49 (36.8)
Unavailable	1 (1)	0	15 (11.3)

IQR = interquartile range; NAC = neoadjuvant chemotherapy; UTSW = University of Texas Southwestern Medical Center.

2.4. Classification of tumors into molecular mRNA subtypes

To assign tumors to the Consensus Bladder Cancer, The Cancer Genome Atlas (TCGA), and LundTax molecular subtypes, we downloaded and applied the centroid-based models as previously described [16–18]. The genomic subtyping classifier (GSC) subtypes were assigned by identifying neuroendocrine (NE)-like tumors and then classifying the remaining tumors using the model of Seiler et al [9,19]. The consensus classifier provided the standard classification of the NE-like subtype. To measure concordance between subtyping classifiers, we sorted each cohort by consensus subtype and presented each model as a column of a subtype-based colored heat map.

2.5. Gene expression analysis

Heat maps and box plots were used to visualize differences between samples from unsupervised consensus clusters (CCs). Sample purity was calculated using the ESTIMATE algorithm [20] and calculations for the other signature scores were as previously described [6,15]. Cases classified as NE-like according to the consensus subtype ($n = 1$ for UTSW, $n = 1$ for PURE-01, and $n = 2$ for NAC), were removed from downstream gene expression analyses, as rigorous evaluation of this rare subtype has identified it as a stand-alone biologic class, lacking expression of basal, luminal, and stromal markers [7,19].

2.6. Statistical analyses

Patient and tumor characteristics were compared between subgroups using χ^2 tests and two-sided Wilcoxon rank-sum tests. The primary endpoint was recurrence-free survival (RFS), which was defined from the time of TURBT until the date of relapse/progression or death from any cause. Patients who were lost to follow-up were censored at the date of last contact. The Kaplan-Meier method was used to estimate the significance of differences in survival curves between patients in different CCs within the cohorts. Tumors classified as NE-like are reported in figure legends for each cohort.

3. Results

The clinical and pathologic features of the UTSW, PURE-01, and NAC patient cohorts are presented in Table 1 [6,11,15]. All PURE-01 and NAC patients had MIBC before treatment, but for 14 patients in the UTSW cohort their clinical non-MIBC was identified at RC as pathologic MIBC.

3.1. Impact of TURBT on molecular subtype at RC without systemic neoadjuvant therapy

To evaluate the impact of TURBT on the molecular subtype of RC samples, we applied the consensus [16], TCGA [17], GSC [9,19], and LundTax [18] subtyping classifiers to residual tumor in RC samples from patients in the NAC ($n = 133$), UTSW ($n = 94$), and PURE-01 ($n = 26$) cohorts. The classifiers were consistent with respect to the basal and luminal axis (consensus reference), but less so with respect to the stromal-rich and NE-like subtypes (Fig. 1A–C). The CC4-scar-like tumors in the NAC cohort were classified as stroma-rich by the consensus model (Fig. 1A and Supplementary Fig. 1), suggesting a similarity between these classifications. Using the consensus classifier, we observed different subtypes in RC samples after immunotherapy in 18 of 22 cases compared to matched pretreatment TURBT samples in the PURE-01 cohort (Fig. 1D). Given the high rate of stroma-rich calls, we next evaluated tumor purity using the ESTIMATE algorithm, finding that the tumor purity decreased and stromal content increased in many cases, suggesting scarring that might be due to TURBT (Supplementary Table 1).

To determine whether TURBT without systemic therapy induced tumor scarring, we performed consensus clustering on the UTSW cohort ($n = 94$) combined with the scar tissue ($n = 21$; total $n = 115$). We selected a three-cluster solution characterized by basal (CC1, $n = 39$), luminal (CC2, $n = 41$), and stromal (CC3, $n = 14$) gene expression profiles (Fig. 2A). As the CC3 group clustered with 19/21 of the scar tissue samples, we next compared the CC3 tumors to scar tissue and found similar profiles, except the scar-like tumors had lower expression of stromal genes (*MYH11*, *DES*, and *C7*; Fig. 2A and Supplementary Fig. 2). The majority of these CC3 tumors were previously classified as stroma-rich (Fig. 2A), consistent with the data for the NAC cohort (Supplementary Fig. 1). Given the similarities of the CC3 tumors to scar tissue, we classified these tumors as CC3-scar-like. These CC3-scar-like tumors showed lower proliferation and tumor purity, but higher EMT, Immune190, and TGF-β signature scores (Fig. 2B–G and Supplementary Fig. 3). Notably, these scar-like tumors were staged as pT2 or pT3 at RC (Supplementary Table 2).

The CC2 cluster was enriched with tumors of the LumP, LumNS, and LumU consensus subtypes (Supplementary

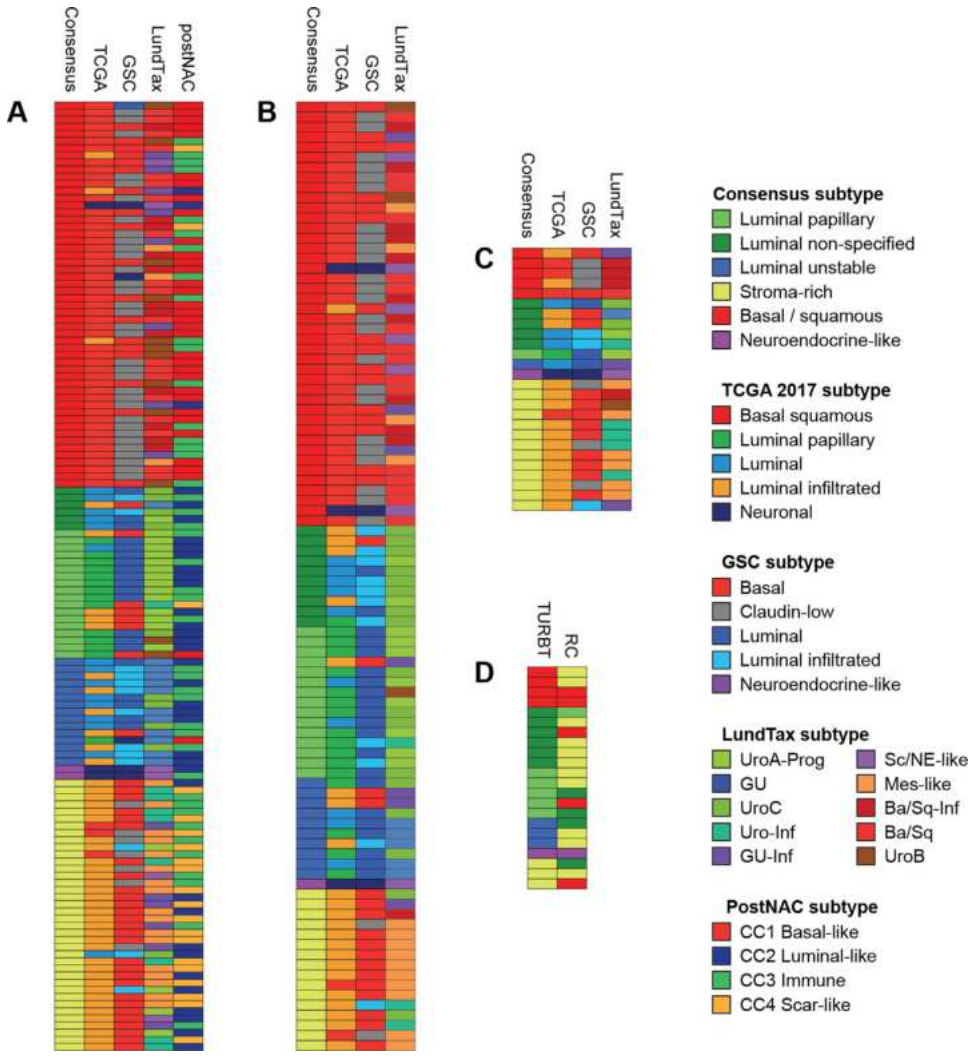

Fig. 1 – Molecular subtyping of radical cystectomy tumor specimens after previous treatment with (A) neoadjuvant chemotherapy (NAC; *n* = 133), (B) no systemic therapy (*n* = 94), and (C) neoadjuvant pembrolizumab (*n* = 26). For the latter cohort, (D) matched transurethral resection of bladder tumor samples were available. Samples were classified according to the Consensus [16], TCGA 2017 [17], GSC [9,19], and LundTax [18] subtyping models. The post-NAC subtypes were determined previously [11]. The order of samples for each cohort is sorted according to the Consensus subtyping model.

Table 3) and consistently expressed high levels of luminal markers (*PPARG*, *GATA3*, and *KRT20*; Fig. 2A and Supplementary Fig. 2), but lower levels of basal markers (*KRT5, KRT14*, and *CD44*; Fig. 2A and Supplementary Fig. 2). These luminal tumors had higher purity and FGFR3 and SHH activity, but lower EMT and immune190 signature scores (Fig. 2B–G and Supplementary Fig. 3). These tumors were predominantly pT2/3 at RC (Supplementary Table 2). Conversely, the CC1 cluster was almost exclusively basal/squamous according to the consensus model and showed the opposite patterns, with higher EMT and Immune190 scores (Fig. 2B–G and Supplementary Fig. 3). The majority of the basal tumors were pT3 and pT4 (Supplementary Table 2). Both the CC1 and CC2 clusters lacked stromal marker expression (Fig. 2A and Supplementary Fig. 2). As the CC1 and CC2 clusters were highly consistent with the basal and luminal subtypes, we named these CC1-Basal and CC2-Luminal, respectively. While the CC1-Basal group showed higher Immune190 scores, we did not identify a strict immune-enriched subtype as was reported for NAC-treated tumors [11].

3.2. *Impact of neoadjuvant pembrolizumab on molecular subtype at RC*

A scar-like class was identified in both platinum-treated (NAC) and RC samples without systemic therapy (UTSW), suggesting that the stroma-rich cases in the PURE-01 cohort might also be scar-like tumors. Given the smaller sample size, PURE-01 ($n = 26$) was combined with the UTSW cohort ($n = 94$) and scar tissues ($n = 21$; total $n = 141$) before performing consensus clustering. Again, we identified a three-cluster solution with basal, luminal, and scar-like classes (Fig. 3A). While the cohorts were unevenly distributed across clusters (χ^2; $p < 0.001$), cohort-level grouping was not apparent within the individual CCs

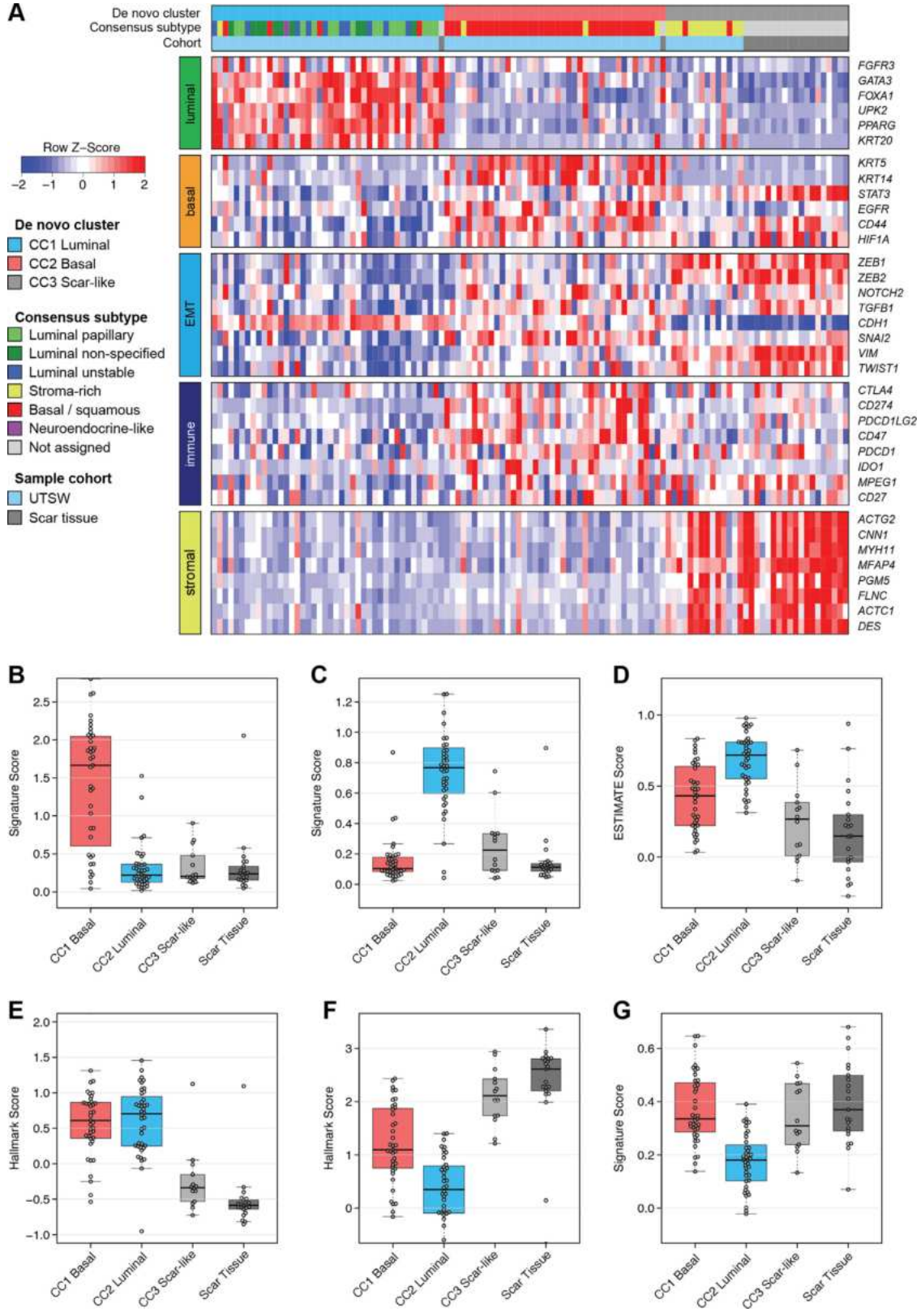

Fig. 2 – Defining novel biological clusters using gene expression profiling in radical cystectomy bladder cancer samples without previous systemic therapy relative to scar tissue. (A) Forced-order heatmap for selected marker genes for muscle-invasive bladder cancer. Signature scores for University of Texas Southwestern (UTSW) consensus clusters (CC1, CC2) compared to scar tissues for (B) basal, (C) luminal, (D) tumor purity, (E) proliferation, (F) epithelial-mesenchymal transition, and (G) Immune190.

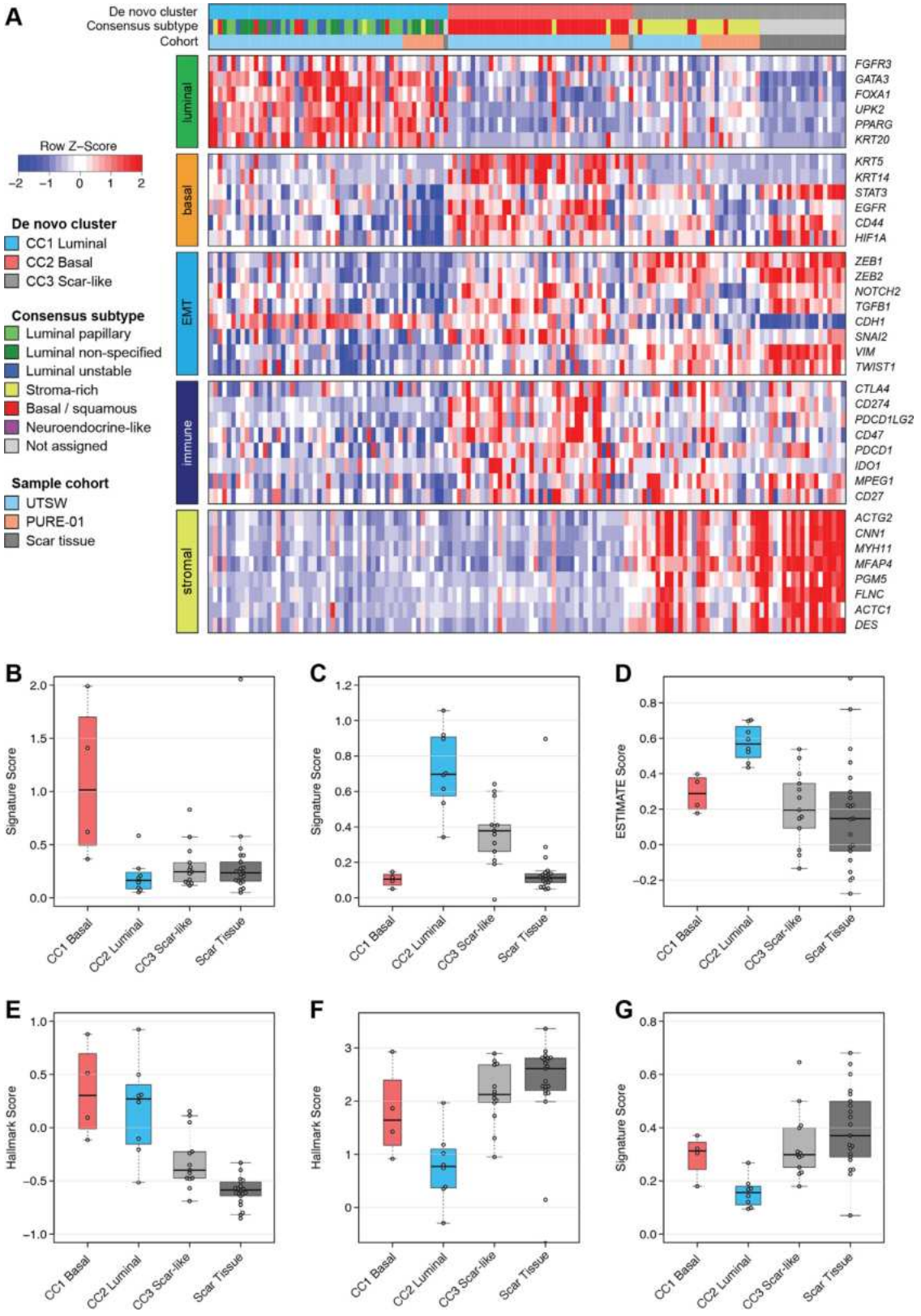

Fig. 3 – Defining novel biological clusters using gene expression profiling in radical cystectomy bladder cancer samples previously treated with neoadjuvant pembrolizumab relative to untreated samples and scar tissue. (A) Forced-order heatmap for selected marker genes for muscle-invasive bladder cancer. UTSW = University of Texas Southwestern. Signature scores for PURE-01 consensus clusters (CC1, CC2) compared to scar tissues for (B) basal, (C) luminal, (D) tumor purity, (E) proliferation, (F) epithelial-mesenchymal transition, and (G) Immune190.

(Supplementary Fig. 4). Tumors from the PURE-01 cohort clustered with the previously defined basal (CC1, $n=4$), luminal (CC2, $n=9$), and scar-like (CC3, $n=13$) cases, revealing that tumor scarring occurred in half (13/26) of post-pembrolizumab RC tumors. As the clustering of the PURE-01 samples was highly consistent with the previous cluster assignments, we retained the CC1-Basal, CC2-Luminal, and CC3-scar like labels (Supplementary Table 4). In the PURE-01 cohort, the majority (12/13) of the scar-like tumors were pT2/T3 (Supplementary Table 2) and only four cases had <50% tumor content (Supplementary Table 5).

The gene expression patterns and signatures for the post-pembrolizumab cluster assignments were similar to those for UTSW, although in the PURE-01 cohort two of the four tumors in the CC1-Basal cluster had lower basal signature scores, suggesting that these may not be as basal-like as the UTSW cases (Fig. 3B). The CC3-scar-like tumors in the PURE-01 cohort had higher luminal signature scores than for the UTSW cases, but these were lower than for CC1-Luminal tumors (Fig. 3C). The remaining signature score patterns were comparable to those for UTSW (Fig. 2B–G). For the PURE-01 samples the signature scores for TGF-β were somewhat higher for the CC2-Luminal type compared to the CC3-scar-like tumors, while the FGFR3 signature was consistent across all clusters (Supplementary Fig. 5). In the PURE-01 cohort, luminal markers were more highly expressed in CC3-scar-like cases compared to the UTSW cohort, while the basal and stromal marker patterns were similar (Supplementary Fig. 6). At TURBT, many tumors were a luminal subtype and were either luminal or scar-like after therapy (Supplementary Fig. 7). Finally, the scar-like tumors tended to have higher angiogenesis signature scores, but lower metabolic and cell cycle activity when compared to the luminal and basal tumors (Supplementary Fig. 8).

On pathology, the CC2-Luminal cluster had no cases with tumor-infiltrating lymphocytes, while the CC1-Basal and CC3-scar-like clusters had 3/4 and 8/13 cases, respectively (Supplementary Table 5). Likewise, all four basal tumors and 11/13 of the CC3-scar-like tumors had evidence of stromal lymphocytic infiltration (Supplementary Table 5). These data were consistent with patterns seen for the Immune190 signature (Fig. 3G). Evidence of inflammation was observed for 5/13 CC3-scar-like cases, with one example from the basal and luminal clusters (Supplementary Table 5). Finally, the luminal tumors were more likely to have angiolymphatic invasion compared to the other clusters (Supplementary Table 5). Representative slides of the tumors from each CC are shown in Supplementary Figure 9.

3.3. Comparison of tumor scar-like subtypes by treatment modality

To determine if systemic therapy induces a unique scar-like profile in RC samples, we performed principal component analysis (PCA) of UTSW, PURE-01, and NAC samples in combination with scar-tissue samples. For UTSW, the CC3-scar-like and scar tissues grouped together, but away from the CC1-Basal and CC2-Luminal tumors (Fig. 4A). The UTSW CC3 scar-like tumors ($n=14$) were then compared to the scar tissues, which revealed highly consistent gene expression profiles (Fig. 4B and Supplementary Table 6). This was aligned with data comparing chemotherapy-treated scar-like tumors to scar tissues, whereby the scar-like samples tended to cluster with scar tissue and few differences were noted (Fig. 4C,D and Supplementary Table 7) [11].

For PURE-01, the CC3-scar-like tumors and scar tissue tended to separate (Fig. 4E). Comparing the CC3-scar-like tumors ($n=13$) from PURE-01 to scar tissue, we noted that many luminal markers (eg, *UPK2*, *GATA3*, *KRT20*, *CDH1*) were upregulated, but stromal makers were downregulated (Fig. 4F, Supplementary Fig. 6, and Supplementary Table 8).

3.4. With systemic therapy, the scar-like subtype has better prognosis

Patients with residual invasive bladder cancer have a worse prognosis than those without [21,22]. In the UTSW cohort, RFS outcomes were poor and did not vary by subtype ($p=0.62$; Fig. 5A). With systemic therapy, the RFS for patients with scar-like tumors was superior to that for patients with basal or luminal tumors (in PURE-01 $p<0.001$; Fig. 5B; and in NAC $p=0.05$; Fig. 5C). In both systemic therapy cohorts, patients with NE-like tumors experienced events within 1 yr (Fig. 5B,C).

3.5. Expression of potential therapeutic targets in RC tissues

For each treatment modality, we identified consistent luminal, basal, and scar-like molecular subtypes. Figure 6 summarizes the distribution of molecular subtypes in residual tumors according to previous treatment. Among the genes that are targets for emerging drugs, we focused on NECTIN4 (*PVRL4*) and TROP2 (*TACSTD2*) as targets of the antibody-drug conjugates enfortumab vedotin and sacituzumab govitecan, respectively. Targets of immunotherapy drugs were also evaluated, including PD-L1 (*CD274*) and PD-1 (*PDCD1*). We found that in all three cohorts, NECTIN4 and TROP2 were most highly expressed in luminal tumors, while PD-L1 and PD-1 were highly expressed in the basal and the NAC immune clusters (Supplementary Fig. 10).

4. Discussion

Current evidence suggests that systemic therapy significantly impacts tumor biology, reflected by dynamic changes in molecular subtype after treatment. The first report of NAC-induced subtype switching identified enrichment in p53-like tumors (MD Anderson Cancer Center [MDA] classification [10]) after treatment, whereby many of these tumors were initially classified as luminal [10]. Detailed molecular characterization of NAC-treated tumors revealed four distinct tumor subtypes post-NAC, including basal, luminal, immune, and a scar-like subtype that was similar to the MDA p53-like subtype [11]. A shift in molecular subtype with treatment is not restricted to NAC but has also been reported in the neoadjuvant immune therapy setting.

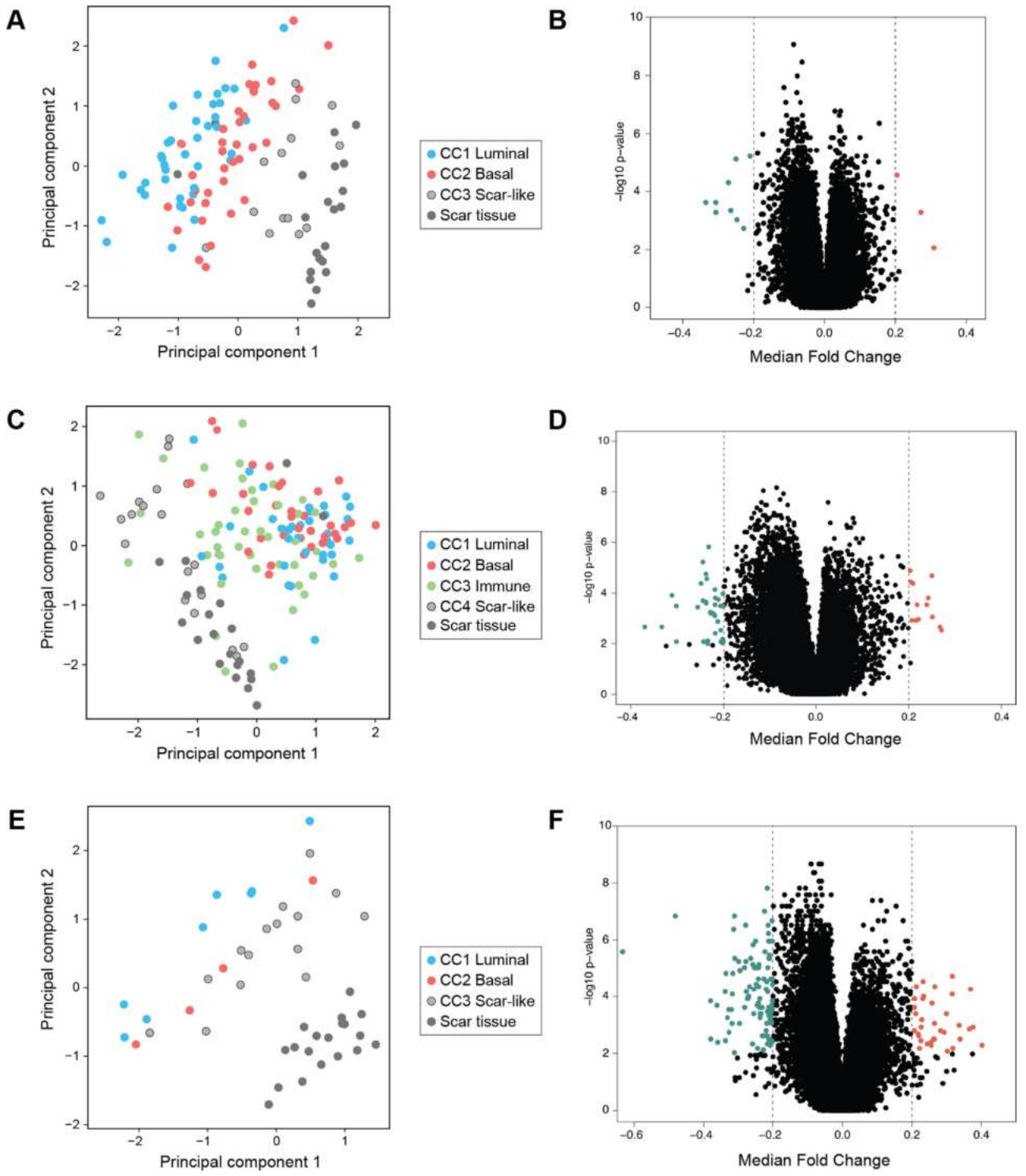

Fig. 4 – Detailed characterization of scar-like tumors across three treatment modalities. (A) Principal component analysis (PCA) for three consensus clusters (CC) with scar tissue for the (A) University of Texas Southwestern (UTSW), (C) neoadjuvant chemotherapy (NAC), and (E) PURE-01 cohorts. Comparison of the median-fold change in gene expression for scar-like cases and scar tissue for the (B) UTSW, (D) NAC, and (F) PURE-01 cohorts. PCA and volcano plots for the NAC cohort have previously been published [11].

In the ABACUS study, 64% of tumors had changed subtype, with enrichment for the infiltrated subtype (Lund classification [14]) [4]. In our study, 71% of post-pembrolizumab tumors were infiltrated according to the Lund 2012 model (data not shown). Notably, all three studies reported a subtype characterized by fibroblast-associated markers, albeit with different nomenclature (p53-like, scar-like, infiltrated).

At present, it is unclear whether fibroblast-associated/scarring transcriptome profiles are induced by systemic

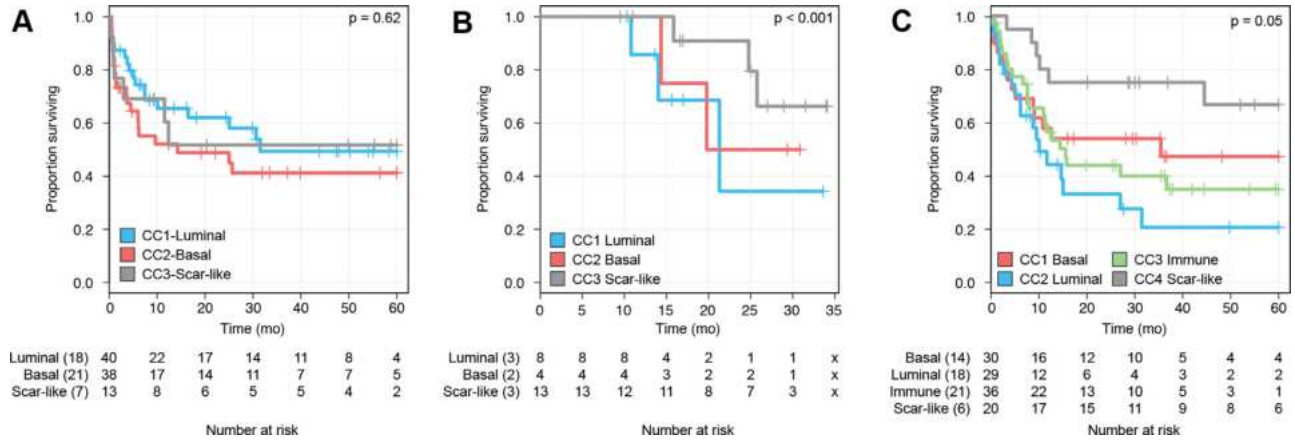

Fig. 5 – Prognosis for patients with residual disease in different treatment settings. Kaplan-Meier plots of recurrence-free survival for (A) untreated (University of Texas Southwestern), (B) pembrolizumab-treated (PURE-01) and (C) chemotherapy-treated (post-neoadjuvant chemotherapy) cohorts. For (B) there was a single patient with a neuroendocrine (NE)-like tumor with an event at 4.5 mo and for (C) there were two patients with NE-like tumors, one with an event at 1.7 mo and one censored at 15.4 mo. The NE-like cases were determined using the consensus classifier.

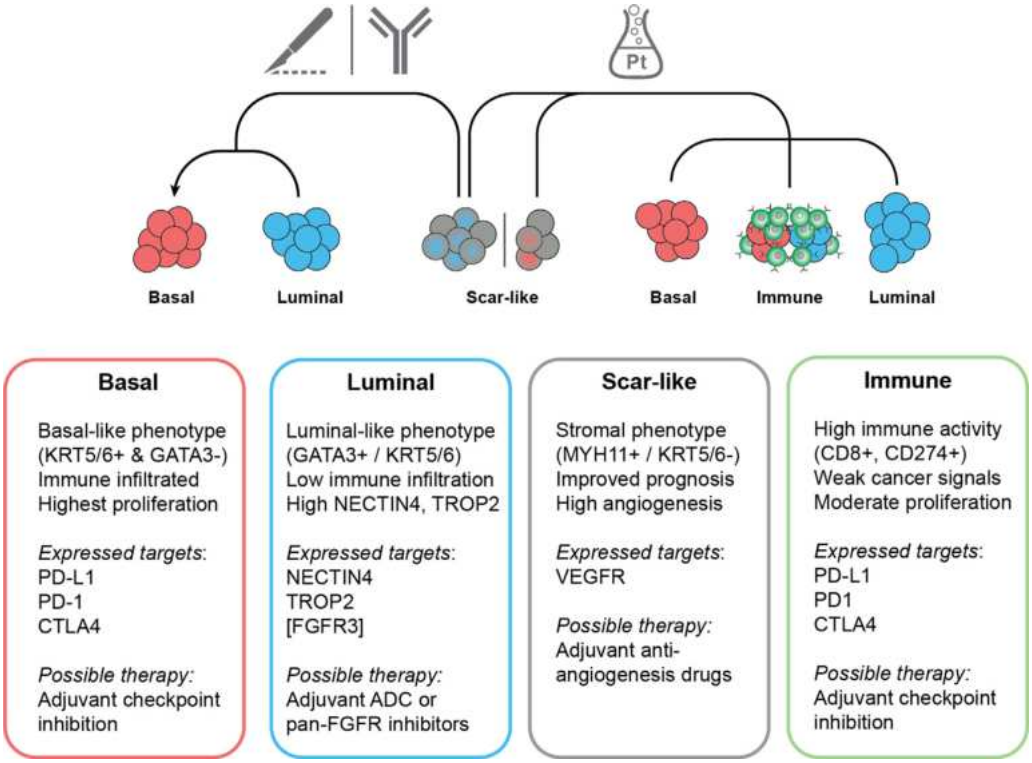

Fig. 6 – Summary figure showing molecular targets and features resulting from the present analyses within each subgroup.

chemotherapy or whether this reflects wound healing in response to TURBT. Cancer-associated fibroblasts are a recognized component of the tumor microenvironment and play a similar role to activated fibroblasts with respect to wound healing [23]. In response to TURBT, fibroblasts in the tumor microenvironment may actively divide and infiltrate the wound site to repair the damage, resulting in cancer-associated scar tissue [23]. In residual tumors treated with either surgery alone or with pembrolizumab, we identified a scar-like subtype with a transcriptome profile that was highly similar to that for non-neoplastic urothelial scar tissue. This scar-like subtype was defined by high expression of stromal markers, high EMT and angiogenesis signatures, and lower tumor purity, consistent with previous observations for NAC-treated tumors [11]. Given the consistency of the scar-like subtype with scar tissue and as TURBT was common to all three cohorts, we hypothesize that TURBT can induce a wound-healing response that results in tumor scarring, which we defined as the scar-like subtype. Of note, in these cohorts, tumors of the scar-like

subtype were predominately of higher tumor stage with a relatively high tumor-cell content and did not appear to be an artifact of tumor sampling.

In the PURE-01 cohort, we observed a high proportion (88/26) of residual tumors classified as luminal and lacking evidence of immune infiltration. Half (13/26) of the RC samples were classified as scar-like, but also expressed luminal markers, distinguishing them from the untreated and NAC-resistant tumors. Using the consensus classifier, many of the TURBT samples were classified as either LumP, LumU, or LumNS, suggesting that luminal tumors may have an intrinsic resistance to checkpoint inhibitor therapy or that pembrolizumab may select for, or induce, a luminal phenotype. This is consistent with the biology of luminal tumors, which have been considered to be non-inflamed or "cold", with lower levels of pre-existing immune infiltration, which may be critical for a robust response to immune checkpoint therapy [6,24]. We did not observe an increase in immune activity after treatment, except in the scar-like tumors post-pembrolizumab. In the larger PURE-01 cohort, favorable pathologic responses (complete or partial) were more often seen for basal-like tumors than for non-basal tumors, but this difference did not reach statistical significance [6].

It remains to be determined through further clinical testing whether the post-therapy subtypes described in this study could be used to select patients for adjuvant treatment. Indeed, the identification of a personalized sequential perioperative approach that is shaped according to the individual's tumor changes during therapy is a primary aim of MIBC treatment. Although we acknowledge that the current assumptions for therapeutic targets are not supported by clinical trial data, in PURE-01 the luminal character of the bulk of the pembrolizumab-treated tumors suggests that these tumors may have a dependency on FGFR3 signaling pathways, making them favorable candidates for FGFR inhibitors such as erdafitinib. However, we did not observe differences in FGFR3 signature scores, although the numbers in this study are relatively small. Conversely, decisions around treatment after chemotherapy may focus on immune therapy for basal or immune subtypes and could favor targeted therapy for the luminal subtypes. For example, we observed higher expression of *NECTIN4* and *TROP2* in post-treatment luminal tumors, each of which is a target for a new antibody-drug conjugate. Interestingly, in biomarker-unselected patients, administration of adjuvant atezolizumab after NAC and surgery has failed to provide an improvement in overall survival over observation alone [25].

Untreated patients could potentially be offered any of the candidate treatments according to their tumor molecular subtype at RC if these are validated as predictors of response to the proposed agents. In all treatment settings, the scar-like tumors have higher angiogenesis activity, suggesting an opportunity for a targeted therapeutic approach with anti-angiogenic therapies based on molecular subtyping of RC tissue. Of course, the caveat to this is whether the tumor itself is actually inducing the scarring [11,26] or if it is a local, normal-tissue healing of the wound site induced by TURBT, and therefore a feature of the tumor microenvironment. However, at present it remains difficult to discern which of these possibilities is correct using transcriptome data for bulk tissue. Other potentially outstanding adjuvant opportunities may be represented by antibody-drug conjugates, especially in the context of luminal tumors post-pembrolizumab therapy.

This hypothesis-generating study has a number of limitations. First, the relative sample size of the PURE-01 cohort is small. Furthermore, we do not have TURBT samples for the untreated tumors so cannot study the evolution of subtypes from TURBT to RC without systemic therapy. Multifocality and intratumor heterogeneity are further inherent limitations of analyses of bulk tumor samples. The cohorts in this study were also combined in several instances; despite similar tissue types, platforms, and normalization methods, we cannot eliminate the influence of all potential confounding variables, particularly given the very different biological nature of the cohorts. We cannot determine whether a switch in subtype after treatment is due to pre-existing tumor heterogeneity and selection of a resistant subtype, or an adaptive change to therapy. Finally, the tumor site sample has the potential to influence the final subtype calls for tumor class, potentially enriching for the scar-like class if a region of lower tumor content, but higher stromal content, is collected.

5. Conclusions

Our study identifies major caveats related to the timing of tumor sampling and the molecular changes associated with treatment. Furthermore, it reinforces our previous finding that treatment results in novel tumor subtypes. In a context in which validated molecular biomarkers are lacking, RC after neoadjuvant systemic therapy has provided an opportunity to streamline biomarker discovery through detailed molecular characterization of residual disease. This study provides a foundation for the development of more tailored treatments beyond immunotherapy in the future.

Author contributions: Ewan A. Gibb 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: Necchi, Gibb.
Acquisition of data: All authors.
Analysis and interpretation of data: Necchi, de Jong, Gibb.
Drafting of the manuscript: Necchi, Gibb.
Critical revision of the manuscript for important intellectual content: All authors.
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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.2021.03.014.

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Platinum Priority – Editorial

Referring to the article published on pp. 149–159 of this issue

When the Molecular Subtype Is Hidden Behind a Veil of Stroma

Gottfrid Sjödahl[a,*], *Fredrik Liedberg*[a], *Mattias Höglund*[b], *Pontus Eriksson*[b]

[a] *Department of Translational Medicine, Division of Urological Research, Lund University, Lund, Sweden;* [b] *Division of Oncology and Pathology, Clinical Sciences, Lund University, Lund, Sweden*

In this issue of *European Urology*, Necchi and colleagues [1] analyze urothelial carcinoma (UC) gene expression profiles in biopsy specimens from transurethral resection of bladder tumor (TURBT) and radical cystectomy (RC) specimens from patients with or without neoadjuvant treatment. The study is a welcome addition to existing data on molecular subtype classification in patient-matched UC biopsies [2–4], an understudied topic. Bladder cancer molecular subtyping has evolved during the past decade, and in this commentary we aim to provide some additional insights regarding the "infiltrated" or "stroma-rich" subtype. We also wish to discuss to what extent a change in subtype can be inferred by comparing a categorical classification of matched biopsies.

With regard to molecular subtype, each nonheterogeneous tumor can be said to have one specific molecular subtype in itself, defined by the objective transcriptomic state of all cells present in the tumor. However, molecular subtyping is performed on biopsy specimens representing only a fraction of the tumor mass. Since the stromal content in different areas of a tumor varies [5], the molecular subtype assigned to a biopsy may differ from the subtype in itself if the cellular proportions in the biopsy specimen are different from those in the whole tumor. Although this may affect any subtype, particular caution is warranted for the unique "infiltrated" or "stroma-rich" subtype defined by high stromal content. While some tumors are naturally stroma-rich, large cohorts will also always yield some biopsy specimens that are stroma-rich due to chance or sampling in the margin of the tumor. Since such "stromal sampling bias" will also result in a stroma-rich subtype, this category as a whole cannot be said to correspond to a subtype in itself. Further insights into the role of the stroma and molecular subtype classification were reported in a recent study on ovarian cancer [6]. The authors used in silico mixing of pure cancer and stroma profiles to show that a small increase in stroma content causes subtype misclassification, and that stromal expression was associated with anatomic sampling location. With this in mind, we would like to suggest alternative interpretations for some of the findings described by Necchi and colleagues [1].

First, the concordance of the consensus molecular subtypes [7] before and after neoadjuvant pembrolizumab in the PURE-01 cohort was described as low, with 18 of 22 cases showing a discordant classification. We note that 12 of the 18 discordant cases changed either to or from the stroma-rich subtype. These cases show a change in stromal content in the biopsy specimens, but for the reasons given above it is not clear whether there was any change in the subtype in itself. The remaining six discordant cases involved four instances with changes between the luminal nonspecified (LumNS) and related luminal-like subtypes, and two from a luminal-like to a basal-squamous classification. Thus, there were ten informative cases not involving the stroma-rich subtype. Out of these ten, two may have changed subtype in itself, four may have changed between luminal-like subtypes, and four did not change subtype. The reason we express uncertainty even after disregarding changes involving the stroma-rich subtype is that we have previously found classification threshold effects to underlie approximately half of all nominal subtype shifts [2]. Thus, minimal absolute differences between two matched profiles, small enough to be just noise, can cause a difference in classification if both samples are "on the border", that is, very close to being classified as another subtype. This situation can be resolved by quantifying the differences

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* Corresponding author. Urological Research Unit, Department of Translational Medicine, Lund University, Scheelevägen 2, 22363 Lund, Sweden. Tel. +46 73 1544949.
E-mail address: gottfrid.sjodahl@med.lu.se (G. Sjödahl).

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between samples in terms of subtype centroid scores and setting a reasonable and minimal absolute difference criterion for discordance.

Next, RC biopsy specimens were combined with tumor-free scar-tissue samples and co-clustering of some tumors with scar-tissue samples was observed. On this basis, tumors were assigned a scar-like subtype which by all accounts appears to be identical to the "stroma-rich" consensus subtype. Undeniably, these biopsies show a stroma-rich profile, and their proportion in the cohort seems normal for this type of study. These biopsy specimens may have become stroma-rich via TURBT-induced tumor scarring, as suggested by the authors, but a more cautious interpretation would allow for the possibility that stromal sampling bias or fragmented residual disease may underlie the changes seen in these samples.

Finally, patients with scar-like tumors had better recurrence-free survival (RFS) in the neoadjuvant- but not in the RC-only cohort. When this finding is discussed in the article, it is suggested that TURBT may induce dynamic molecular changes resulting in a treatment-responsive and scar-like biology unique to RC samples. Such causality may be difficult to claim given that every patient had their bladder removed and that any effect on RFS in the neoadjuvant setting is by definition related to treatment effects on microscopically disseminated disease. While we cannot rule out that micrometastatic disease may follow the same dynamic scar-like changes as seen in the bladder, we suggest an alternative explanation for the better RFS for patients with scar-like tumors. Suppose that RC specimens from responders, that is, patients with a low residual cancer burden in the RC specimen, also have on average less cancer in their biopsy specimens compared to cases with extensive residual cancer. Since there are only cancer cells and stromal cells in a biopsy specimen, this average decrease in cancer cell content implies a corresponding increase in stromal content, which may cause biopsies to become classified as scar-like.

Although we may interpret some of the results differently, we thank the authors for making gene expression data from clinical trials and cohorts available for the research community and for engaging in stimulating discussion on the nature of molecular subtypes of UC.

Conflicts of interest: The authors have nothing to disclose.

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Platinum Priority – Kidney Cancer

Editorial by Daniel M. Geynisman and Elizabeth R. Plimack on pp. 171–173 of this issue

A Single-arm, Multicenter, Phase 2 Study of Lenvatinib Plus Everolimus in Patients with Advanced Non-Clear Cell Renal Cell Carcinoma

Thomas E. Hutson [a,*], *M. Dror Michaelson* [b], *Timothy M. Kuzel* [c], *Neeraj Agarwal* [d], *Ana M. Molina* [e], *James J. Hsieh* [f], *Ulka N. Vaishampayan* [g], *Ran Xie* [h], *Urmi Bapat* [h], *Weifei Ye* [i], *Rohit K. Jain* [j], *Mayer N. Fishman* [k]

[a] *Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA;* [b] *Massachusetts General Hospital Cancer Center, Boston, MA, USA;* [c] *Rush University Medical Center, Chicago, IL, USA;* [d] *Huntsman Cancer Center, (NCI-CCC), University of Utah, Salt Lake City, UT, USA;* [e] *Weill Cornell Medicine, New York, NY, USA;* [f] *Washington University School of Medicine, St. Louis, MO, USA;* [g] *Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA;* [h] *Eisai Inc., Woodcliff Lake, NJ, USA;* [i] *Green Key Resources, LLC, New York, NY USA;* [j] *H. Lee Moffitt Cancer Center, Tampa, FL, USA;* [k] *Cancer Center of South Florida, Tampa, FL, USA*

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Abstract

Background: Non-clear cell renal cell carcinoma (nccRCC) accounts for ≤20% of RCC cases. Lenvatinib (a multitargeted tyrosine kinase inhibitor) in combination with everolimus (an mTOR inhibitor) is approved for the treatment of advanced RCC after one prior antiangiogenic therapy.
Objective: To determine the safety and efficacy of lenvatinib plus everolimus as a first-line treatment for patients with advanced nccRCC.
Design, setting, and participants: This open-label, single-arm, multicenter, phase 2 study enrolled patients with unresectable advanced or metastatic nccRCC and no prior anticancer therapy for advanced disease.
Intervention: Lenvatinib (18 mg) plus everolimus (5 mg) orally once daily.
Outcome measurements and statistical analysis: The primary endpoint was the objective response rate (ORR) as assessed by investigators according to Response Evaluation Criteria in Solid Tumors version 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety assessments. The 95% confidence intervals (CIs) for ORRs were calculated using the two-sided Clopper-Pearson method. Median PFS and median OS were estimated using the Kaplan-Meier product-limit method and their 95% CIs were estimated via a generalized Brookmeyer and Crowley method.
Results and limitations: The study (start date: February 20, 2017) enrolled 31 patients with nccRCC (papillary, $n = 20$; chromophobe, $n = 9$; unclassified, $n = 2$). At the data cutoff date (July 17, 2019), the best overall response was a partial response (eight patients: papillary, $n = 3$; chromophobe, $n = 4$; unclassified, $n = 1$) for an overall ORR of 26% (95% CI 12–45). Median PFS was 9.2 mo (95% CI 5.5–not estimable), and median OS was 15.6 mo (95% CI 9.2–not estimable). The most common treatment-emergent adverse events were fatigue (71%), diarrhea (58%), decreased appetite (55%), nausea (55%), and vomiting (52%). Limitations include the small sample size and single-arm design.

* Corresponding author. Texas Oncology-Baylor Charles A. Sammons Cancer Center, 3410 Worth Street, Suite 400, Dallas, TX 75254, USA. Tel.: +1 214 370 1000.
E-mail address: thomas.hutson@usoncology.com (T.E. Hutson).

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Conclusions: Lenvatinib plus everolimus showed promising anticancer activity in patients with advanced nccRCC with an ORR of 26% and is worthy of further study. The safety profile was consistent with the established profile of the study-drug combination.
Patient summary: We examined the combination of lenvatinib plus everolimus as the first therapy for 31 patients who had advanced nccRCC. We found that this treatment seemed effective, because most patients had a decrease in tumor size and manageable treatment-related side effects.
Clinical registration: This trial is registered at ClinicalTrials.Gov as NCT02915783.

1. Introduction

Renal cell carcinoma (RCC) is generally grouped into two principal subtypes: clear cell RCC (ccRCC), which accounts for more than 80% of RCC cases, and non-clear cell RCC (nccRCC), an umbrella term that encompasses the remaining histological subtypes [1]. The histological subtypes that fall under the nccRCC designation include papillary RCC, chromophobe RCC, unclassified RCC, collecting duct carcinoma, and renal medullary carcinoma, among others [1,2].

Historically, the majority of RCC clinical trials have focused on ccRCC or mixed RCC populations. However, over the past five years, studies have begun to specifically enroll patients with nccRCC, and treatments with single-agent VEGF and mTOR inhibitors have been assessed in this patient population. Disappointingly, compared to the response rates observed for patients with ccRCC, these studies reported low response rates, with overall objective response rates (ORRs) ranging from 3% to 18% [3,4].

The mTOR pathway has been implicated in the pathogenesis of RCC, with mutations in this pathway occurring at a frequency of approximately 5% in both the chromophobe and papillary subtypes of nccRCC [5]. A phase 2 clinical study of patients with nccRCC and no prior systemic therapy compared the effectiveness of sunitinib (a VEGF-targeted tyrosine kinase inhibitor [TKI]) and the mTOR inhibitor, everolimus [3]. Interestingly, among patients with chromophobe nccRCC in the study, 33% ($n = 2/6$) had an objective response to everolimus treatment, compared to 10% ($n = 1/10$) with sunitinib. By contrast, patients with papillary nccRCC fared better with sunitinib treatment than with everolimus, with ORRs of 24% ($n = 8/33$) and 5% ($n = 2/37$), respectively [3]. In a phase 2 clinical study of 34 patients with different histologic subtypes of nccRCC treated with a combination of bevacizumab and everolimus, the ORR was 29% [6]. Taken together, these data suggest that both VEGF- and mTOR-directed agents may be effective therapies for multiple nccRCC subtypes and further study is warranted.

Lenvatinib, in combination with everolimus, is approved for the treatment of patients with advanced RCC following one prior antiangiogenic therapy [7]. Lenvatinib is a multitargeted TKI of VEGF receptors 1–3, FGF receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT [8–11]. The combination of lenvatinib plus everolimus has shown enhanced antitumor activity in patients with RCC [12,13] in both clinical and real-world settings [13,14]. Preclinical experiments have demonstrated that lenvatinib plus everolimus yields enhanced inhibition of both VEGF- and FGF-driven angiogenesis that is greater than for either agent alone [15]. Thus, it is hypothesized that dual inhibition of both the VEGF- and FGF-driven pathways, and downstream mTOR pathways, using the combination of lenvatinib plus everolimus, may contribute to the enhanced inhibition of both angiogenic and proliferation pathways in RCC [12,15].

While both VEGF-targeted TKIs and everolimus have shown some promise as monotherapies for nccRCC, it is not known whether targeting both pathways simultaneously will confer a greater benefit for these patients. This phase 2 single-arm, multicenter study evaluated the safety and efficacy of lenvatinib (18 mg once daily) plus everolimus (5 mg once daily) in patients with unresectable advanced or metastatic nccRCC who had not received any prior anticancer therapy for advanced disease.

2. Patients and methods

2.1. Study design and patients

This phase 2 single-arm, multicenter study enrolled patients with histologically confirmed nccRCC (per study investigator), measurable disease per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), and no prior anticancer therapy for advanced disease. Eligible patients must have had one of the following types of nccRCC: papillary, chromophobe, collecting duct carcinoma, renal medullary carcinoma, or unclassified RCC. In addition, eligible patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, adequate liver, renal, and bone marrow function, and adequately controlled blood pressure (≤140/90 mm Hg). Patients were excluded according to the following key criteria: predominantly ccRCC, prior exposure to lenvatinib or an mTOR inhibitor, or major surgery ≤3 wk from the starting dose. Patients were also excluded if they had uncontrolled diabetes, proteinuria (urine protein, ≥1 g/24 h), interstitial lung disease or active noninfectious pneumonitis, or any condition that would affect the absorption of the study-drug combination.

Enrolled patients received lenvatinib (18 mg orally once daily) plus everolimus (5 mg orally once daily) in continuous 28-d cycles. Patients continued to receive one or both study drugs for as long as evidence of clinical benefit was present, or until intercurrent illness, unacceptable toxicity, disease progression, or withdrawal of patient consent.

The study was conducted in full accordance with the International Conference on Harmonization Good Clinical Practice guidelines and federal regulations. The protocol was approved by the institutional review board or independent ethics committee in each center. Written informed consent was obtained from all study participants before study enrollment. This trial is registered at ClinicalTrials.Gov as NCT02915783.

2.2. Study endpoints and assessments

The primary endpoint was the ORR as assessed by investigators using RECIST v1.1. Confirmation of complete response and partial response was required ≥4 wk after a response was first documented. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). PFS and ORR by independent imaging review (IIR) were also assessed as exploratory endpoints. Additional exploratory endpoints included the clinical benefit rate (CBR; defined as the proportion of patients with a best overall response of complete response, partial response, or durable [≥23 wk] stable disease) and the disease control rate (DCR; defined as the proportion of patients with a best overall response of complete response, partial response, or stable disease). Tumor assessments were performed according to RECIST v1.1, with imaging studies carried out every 8 wk (±1 wk) after the first dose of study treatment.

Safety was assessed by monitoring and recording all adverse events, including all grades according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

2.3. Statistical analysis

At the time of study protocol development, the response rates for patients with nccRCC treated with the study drugs (lenvatinib and everolimus, either as monotherapies or in combination) were not available. The sample size for the study was calculated using Simon's two-stage design for the primary endpoint of ORR assuming an ORR of 25% from this study versus a historical control of 8% for patients with advanced RCC [16]. A total of approximately 31 patients, including 16 in stage 1, were planned to be enrolled in the study. If there were one or no responders in stage 1, the enrollment would be stopped; if there were two or more responders, the study would proceed to stage 2. At interim analysis, based on an assumption of ORR = 8% for the null hypothesis and ORR ≥ 25% for the alternative hypothesis, the probability of early futility stopping was 0.6299 and 0.0635, respectively. This design would yield a one-sided type I error of 0.0319 and power of 0.8053 in stages 1 and 2 combined. In the final analysis, if six of 31 patients were considered responders, then the study ORR would be considered statistically significant compared with historical controls.

The 95% confidence intervals (CIs) for response rates were calculated using the two-sided Clopper-Pearson method. Median PFS and median OS were estimated using the Kaplan-Meier product-limit method and their 95% CIs were estimated with a generalized Brookmeyer and Crowley method.

3. Results

This phase 2 study enrolled 31 patients with nccRCC, all of whom received the study treatment. Most patients had papillary type (n = 20/31; 65%), followed by chromophobe, (n = 9/31; 29%), and unclassified (n = 2/31; 6%) nccRCC. Among the enrolled patients, the median age was 64 yr, and approximately two-thirds were men (65%). Most patients had an ECOG PS of 0 (n = 23/31; 74%), and fewer than half had undergone a prior nephrectomy (n = 11/31; 35%). Lymph nodes were the most common site of metastasis (n = 22/31; 71%; Table 1).

By the data cutoff date (July 17, 2019), 25 patients (81%) had discontinued the study treatment and six (19%) remained on treatment. The following reasons led to study-drug discontinuation: radiological or clinical disease progression (n = 15/31; 48%), adverse event (n = 6/31; 19%), or patient choice (n = 4/31; 13%). Among the 25 patients who discontinued treatment, eight remained on study follow-up for OS.

Table 1 – Baseline patient demographics and disease characteristics for the 31 study participants

Parameter	Result
Median age, yr (range)	64 (38–85)
Males, *n* (%)	20 (65)
Race, *n* (%)	
White	27 (87)
Black or African American	1 (3)
Other	3 (10)
ECOG performance status 0, *n* (%) [a]	23 (74)
Histology, *n* (%)	
Papillary	20 (65)
Chromophobe	9 (29)
Unclassified	2 (6)
Sites of metastases at baseline, *n* (%)	
Adrenal	4 (13)
Bone	7 (23)
Liver	9 (29)
Lung	8 (26)
Lymph node	22 (71)
Other	11 (35)
Number of metastatic sites, *n* (%)	
0	0
1	12 (39)
2	10 (32)
≥3	9 (29)
Prior nephrectomy, *n* (%)	11 (35)
IMDC prognostic group at baseline, *n* (%)	
Favorable risk	4 (13)
Intermediate risk	20 (65)
Poor risk	7 (23)

ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.
[a] The remaining patients had ECOG performance status of 1, in accordance with the protocol.

A best overall response of partial response was observed in eight patients and no patients had a confirmed complete response (Fig. 1 and Table 2). The overall ORR was 26% (95% CI 12–45), both when assessed by an investigator and by IIR. As assessed by an investigator, stable disease was observed in 18 patients, for a DCR (complete response, partial response, or stable disease) of 84%, and durable (≥23 wk) stable disease was observed in 11 patients, for a CBR (complete response, partial response, or durable stable disease) of 61%. By comparison, the DCR and CBR by IIR were 71% and 52%, respectively (Table 2). The median duration of response was not estimable (NE); however, per IIR, the majority (88%) of responders (ie, those with complete or partial responses) had maintained their response for 5 mo.

Among 20 patients with papillary RCC, three had partial responses, for an ORR of 15% (n = 3/20), and an additional 14 patients had stable disease, for a DCR of 85% (n = 17/20; as assessed by investigator). A best overall response of partial response was observed in four patients with chromophobe nccRCC, resulting in an ORR of 44% (n = 4/9), and an additional three patients had stable disease, for a DCR of 78% (n = 7/9; as assessed by an investigator). Of the two patients in this study with unclassified nccRCC, one had a partial response and one had stable disease.

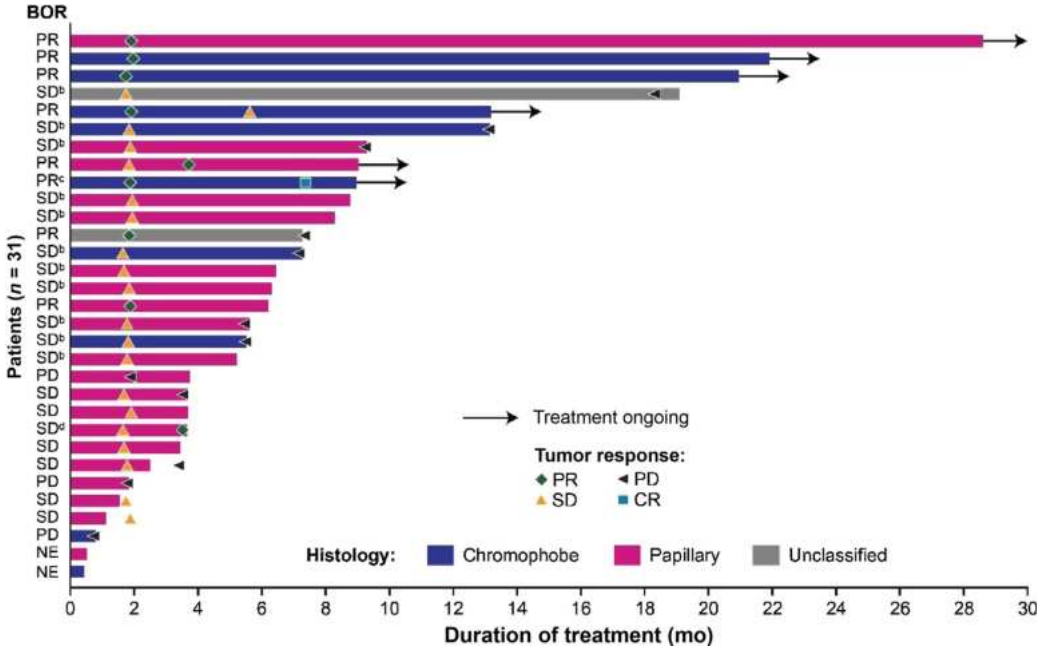

Fig. 1 – Duration of treatment and tumor response by investigator assessment according to Response Evaluation Criteria in Solid Tumors version1.1.[a]
BOR = best overall response; CR = complete response; PD = progressive disease; PR = partial response; NE = not evaluable; SD = stable disease.
[a] The figure indicates the outcome at a patient's first tumor assessment and then any subsequent change in tumor response status.
[b] These patients had durable stable disease.
[c] This patient had a complete response, but this response was not confirmed by the time of data cut-off, so the BOR for this patient is a partial response.
[d] This patient had stable disease at first assessment and a subsequent partial response; since the partial response was not confirmed because of treatment discontinuation (patient's choice), the BOR for this patient is stable disease.

Table 2 – Summary of efficacy outcomes by histological subtype

Parameter	By investigator assessment				By IIR
	Papillary (*n* = 20)[a]	Chromophobe (*n* = 9)[a]	Unclassified (*n* = 2)[a]	Total (*n* = 31)	Total (*n* = 31)
Objective response rate, *n* (%) (95% CI) [b]	3 (15) (3–38)	4 (44) (14–79)	1 (50) (1–99)	8 (26) (12–45)	8 (26) (12–45)
Best overall response, *n* (%)					
Complete response	0	0	0	0	0
Partial response	3 (15)	4 (44)	1 (50)	8 (26)	8 (26)
Stable disease	14 (70)	3 (33)	1 (50)	18 (58)	14 (45)
Durable stable disease [c]	7 (35)	3 (33)	1 (50)	11 (35)	8 (26)
Progressive disease	2 (10)	1 (11)	0	3 (10)	6 (19)
Not evaluable/unknown	1 (5)	1 (11)	0	2 (6)	3 (10)
Clinical benefit rate, n (%) [d]	10 (50)	7 (78)	2 (100)	19 (61)	16 (52)
(95% CI) [b]	(27–73)	(40–97)	(16–100)	(42–78)	(33–70)
Disease control rate, n (%) [e]	17 (85)	7 (78)	2 (100)	26 (84)	22 (71)
(95% CI) [b]	(62–97)	(40–97)	(16–100)	(66–95)	(52–86)
Median PFS, mo (95% CI)[f,g]	9.2 (3.5–NE)	13.1 (0.5–NE)	12.8 (7.3–18.3)	9.2 (5.5–NE)	5.6 (3.5–NE)
Median OS, mo (95% CI) [f,g]	11.7 (8.1–NE)	NE (0.5–NE)	NE (NE–NE)	15.6 (9.2–NE)	NA

CI = confidence interval; IIR = independent imaging review; NA = not applicable; NE = not estimable; OS = overall survival; PFS = progression-free survival.
[a] Percentages for the histological subtypes (papillary, chromophobe, and unclassified) are based on the number of patients with that subtype.
[b] The 95% CI was calculated using the two-sided Clopper-Pearson method.
[c] Durable stable disease = duration ≥23 wk.
[d] Clinical benefit rate = complete response + partial response + durable stable disease.
[e] Disease control rate = complete response + partial response + stable disease.
[f] Median PFS and OS were estimated using the Kaplan-Meier product-limit method and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method.
[g] Given the small sample size, results should be interpreted with caution.

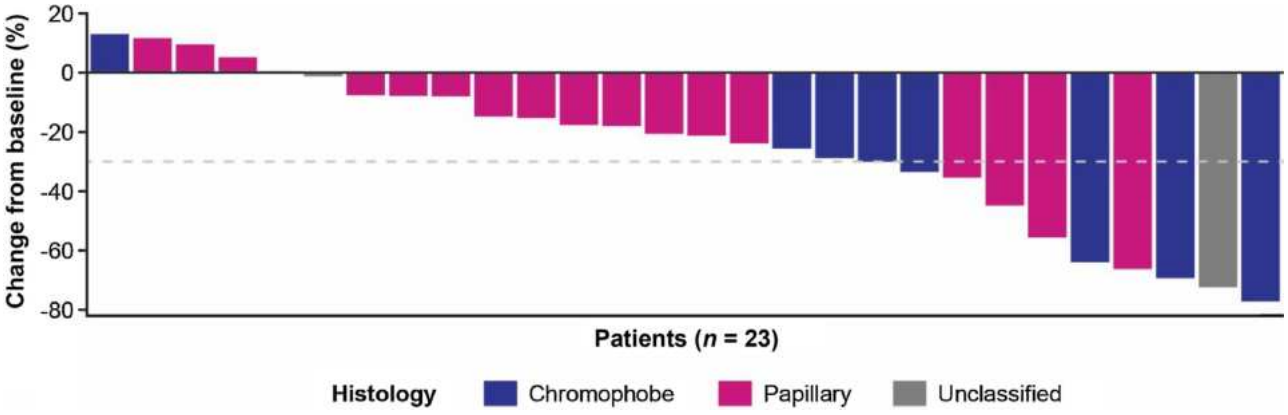

Fig. 2 – Percentage change in total sum of target lesion diameters from baseline to postbaseline nadir by investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1. The analysis included patients with both baseline and at least one postbaseline target lesion assessment.

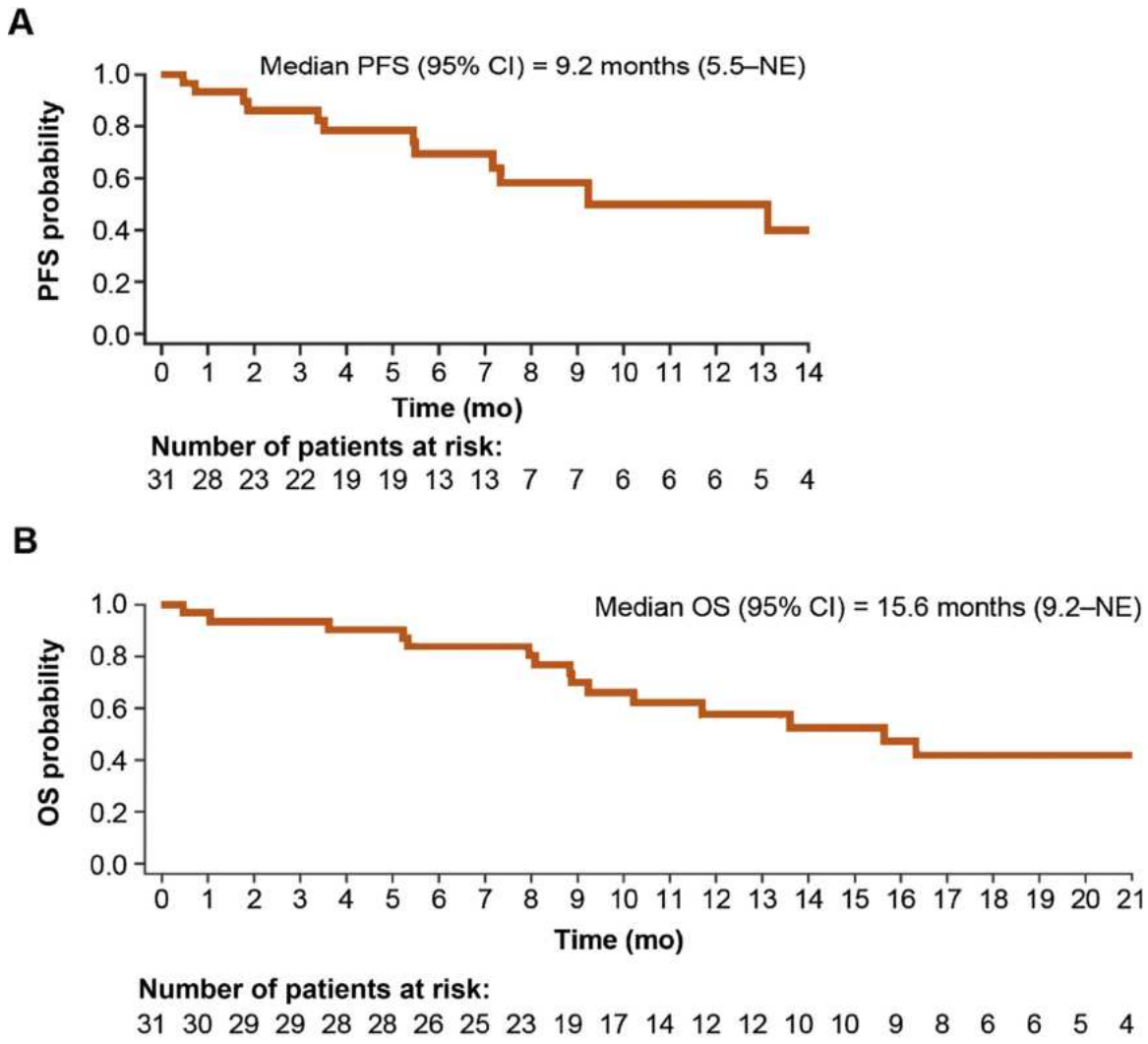

Fig. 3 – Kaplan-Meier estimates of (A) PFS and (B) OS by investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1. The survival estimates were truncated when fewer than five patients at risk remained.
CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression-free survival.

Most patients had a decrease in tumor size both by investigator assessment (Fig. 2) and by IIR (Supplementary Fig. 1). The median PFS was 9.2 mo (95% CI 5.5–NE) by investigator assessment (Fig. 3A) and 5.6 mo (95% CI 3.5–NE) by IIR. Median OS was 15.6 mo (95% CI 9.2–NE; Fig. 3B). The median PFS by investigator assessment and OS outcomes by histological subtypes are shown in Table 2.

All 31 patients experienced at least one treatment-emergent adverse event (TEAE). The five most common TEAEs (any grade) were fatigue (71%), diarrhea (58%), decreased appetite (55%), nausea (55%), and vomiting (52%; Table 3). TEAEs of grade ≥3 severity occurred in 68% of patients (n = 21/31). TEAEs led to study-drug discontinuation or withdrawal by 32% of patients (n = 10/31; one each for cardiac arrest, cardiac failure, arthralgia, back pain, cancer pain, hepatic encephalopathy, and tremor; and three for malignant neoplasm progression). TEAEs led to a dose reduction (lenvatinib only) in 45% (n = 14/31), and study-drug interruption (lenvatinib and/or everolimus) in 68% (n = 21/31) of patients. Overall, patients had a median relative dose intensity of 87% (range 32–100%) for lenvatinib and 94% (range 64–100%) for everolimus.

Overall, treatment-related TEAEs (all grades) occurred in 94% of patients, and 48% (n = 15/31) of patients had at least one treatment-related TEAE of grade ≥3 severity. Although there were three fatal TEAEs (malignant neoplasm progression, n = 2; cardiac arrest, n = 1), these were assessed as not related to treatment by the investigators.

Table 3 – Treatment-emergent adverse events (TEAEs) occurring in ≥15% of the 31 patients

TEAE, Preferred Term [a]	Patients, n (%)	
	Any grade	Grade ≥3
Fatigue	22 (71)	2 (6)
Diarrhea	18 (58)	3 (10)
Decreased appetite	17 (55)	0
Nausea	17 (55)	2 (6)
Vomiting	16 (52)	2 (6)
Stomatitis	12 (39)	0
Weight decreased	12 (39)	0
Hypertension	10 (32)	5 (16)
Abdominal pain	9 (29)	1 (3)
Dyspnea	8 (26)	0
Epistaxis	8 (26)	0
Headache	8 (26)	0
Insomnia	8 (26)	0
Proteinuria	8 (26)	2 (6)
Arthralgia	7 (23)	0
Back pain	7 (23)	1 (3)
Dysphonia	7 (23)	0
Anxiety	6 (19)	0
Blood creatinine level increased	6 (19)	0
Constipation	6 (19)	0
Dyspepsia	6 (19)	0
Nasal congestion	6 (19)	0
Cough	5 (16)	0
Dizziness	5 (16)	0
Hypothyroidism	5 (16)	0
Malignant neoplasm progression	5 (16)	4 (13)
Muscular weakness	5 (16)	0
Pruritus	5 (16)	0

[a] Adverse event terms were coded using Medical Dictionary for Regulatory Activities version 22.0 and graded using Common Terminology Criteria for Adverse Events version 4.03.

4. Discussion

This phase 2 study demonstrated that the combination of lenvatinib plus everolimus showed promising antitumor activity as a potential first-line therapy for patients with advanced nccRCC, with an overall ORR of 26% (both by investigator assessment and by IIR). The observed overall ORR of 26% in this study meets the prespecified threshold for statistical significance compared to historical controls of patients with advanced RCC (available at the time of study protocol development). Moreover, the ORR of 26% compares favorably to current response rates reported for patients with nccRCC who were treated with everolimus monotherapy (9%) [3]. While no ORRs have been reported to date for patients with nccRCC who were treated with single-agent lenvatinib, the observed ORR (26%) appears higher than that seen with other single-agent TKIs (ie, sunitinib; ORRs range from 9% to 18% [3,4]) and comparable to overall ORRs reported for patients with nccRCC in response to immunotherapy (ORRs range from 10% to 26% [17–21]). While no confirmed complete responses were observed in this study, partial responses were observed in patients across all histological subtypes enrolled (papillary, chromophobe, and unclassified nccRCC).

Historically, ORRs for patients with nccRCC have been low (3–18%) [3,4]. Thus, more recent studies have been aimed at improving outcomes in these patients. Retrospective analyses for both cabozantinib and nivolumab have shown some potential in patients with nccRCC, with overall ORRs of 22–27% recorded [17,22]. However, prospective studies for cabozantinib in nccRCC are still lacking. Moreover, a clinical trial among patients with nccRCC who were treated with nivolumab demonstrated a range of responses based on histological subtypes (ORRs ranging from 0% to 25%) [18], suggesting that response to nivolumab may be subtype-specific. Similarly, in a recent single-arm, phase 2 study of first-line pembrolizumab among 165 patients with nccRCC (KEYNOTE-427B) [19], the ORRs observed ranged between 10% and 31% for different histological subtypes.

Additional studies have been conducted in patients with specific papillary nccRCC subtypes. Srinivasan et al [23] reported on a phase 2 study of patients with type 2 papillary nccRCC who were treated with bevacizumab and erlotinib, and demonstrated an ORR of 51% (n = 42/83; 95% CI 40–61). The phase 3 SAVIOR trial, which assessed the efficacy of savolitinib (a MET-kinase inhibitor) versus sunitinib in patients with metastatic MET-driven papillary nccRCC, reported an ORR of 27% (n = 9/33; 95% CI 13–46) in the savolitinib treatment arm and an ORR of 7% (n = 2/27; 95% CI 1–24) in the sunitinib arm [24]. While these data appear promising for patients with these specific subtypes of nccRCC (eg, type 2 papillary or MET-driven papillary), additional therapies are still needed for patients with histological subtypes that were not investigated in these trials. Moreover, enrollment in clinical trials is still a

recommended treatment option for patients with nccRCC [25]; consequently, further prospective studies are warranted for patients with nccRCC to identify better treatments across histological subtypes.

Among 20 patients with papillary histology treated with lenvatinib plus everolimus in the current study, three had partial responses for an ORR of 15% (n = 3/20; 95% CI 3–38). By comparison, an ORR of 24% was observed in papillary nccRCC treated with single-agent sunitinib [3]. Notably, in our study four patients with chromophobe nccRCC had a partial response for an ORR of 44% (n = 4/9; 95% CI 14–79), and one of the two patients with unclassified histology also had a partial response. By comparison, in the KEYNOTE 427B study [19], promising ORRs of 28% (95% CI 20–37) and 31% (95% CI 14–52) were observed for papillary and unclassified nccRCC subtypes, respectively· However, a lower ORR of 10% (95% CI 1–30) was observed for the chromophobe histological subtype. Taken together, the data in the current study suggest that the combination of lenvatinib plus everolimus may hold promise across histological subtypes, with some subtypes appearing to derive more benefit. The subtypes that respond best to PD-1–targeted immunotherapy versus the multitargeted lenvatinib plus everolimus combination appear divergent, which suggests that further studies may be warranted to distinguish between these agents and the nccRCC subtypes that would benefit the most from these treatments.

Particularly noteworthy in this study is the promising ORR of 44% (n = 4/9; 95% CI 14–79) and CBR of 78% (n = 7/9; 95% CI 40–97) for patients with chromophobe nccRCC. Although this study is limited by its small sample size (n = 31 overall and n = 9 for the chromophobe histology) and cross-study comparisons have inherent limitations, these results compare favorably to the ORRs ranging from 10% to 33% observed among patients with chromophobe nccRCC with single-agent sunitinib or everolimus treatment in the ASPEN study [3]. Moreover, the ORR of 44% in the current study is higher than the ORR range of 0–10% for patients with chromophobe nccRCC treated with immunotherapy [17–19].

The mTOR pathway has been implicated in the development of chromophobe nccRCC. Patients with Birt-Hogg-Dube syndrome develop a hereditary form of chromophobe nccRCC characterized by the development of tumors with highly active PI3K/mTOR pathways [26]. While further studies may be needed to fully delineate the mechanism of action that accounts for the apparent enhanced anticancer activity of lenvatinib plus everolimus in this histological subtype, our study results are consistent with the hypothesis that dual inhibition of both the VEGF- and FGF-driven pathways, as well as downstream mTOR pathways, by this combination [12,15], leads to enhanced antitumor activity in patients with nccRCC. In addition, as the mTOR pathway is implicated in the pathogenesis of chromophobe nccRCC, inhibition of mTOR via everolimus may account for the enhanced anticancer activity observed in this subtype in the current study.

With respect to the secondary endpoints in the current study, treating patients with nccRCC with lenvatinib plus everolimus resulted in an overall median OS of 15.6 mo, which was similar to that observed with first-line treatment with single-agent sunitinib (16.2 mo) or everolimus (14.9 mo) [4]. While the median OS was similar, the median PFS of 9.2 mo was encouraging and appeared prolonged compared with that observed with first-line sunitinib (6.1 mo) or everolimus (4.1 mo) treatment [4]. Moreover, it is noteworthy that the median PFS was 9.2 mo in the current study, even though 61% of patients had two or more sites of metastases and the majority of patients (87%) were in the intermediate or poor prognostic risk group.

Given the pathways involved in nccRCC and the mechanisms of action of lenvatinib and everolimus, further applied development of these combined agents and combinations of agents with other mechanisms, such as anti–PD-1/L1 plus anti–CTLA4 antibodies or anti–PD-1/L1 agents plus VEGF inhibitors remain of interest.

5. Conclusions

This open-label, phase 2 study of the combination of lenvatinib plus everolimus as a first-line treatment for patients with advanced or metastatic nccRCC achieved an ORR of 26% (95% CI 12–45) by both investigator assessment and IIR, with an ORR of 44% among patients with chromophobe histology. The combination demonstrated encouraging anticancer activity, with a median OS of 15.6 mo, and median PFS of 9.2 mo by investigator assessment and 5.6 mo by IIR. The tolerability profile observed in this study was similar to the established safety profiles of the study-drug combination in RCC [13], with no new safety signals. Cumulatively, these data suggest that the combination of lenvatinib plus everolimus has promising anticancer activity and is worthy of future study in patients with nccRCC.

Author contributions: Thomas E. Hutson 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: Hutson, Xie, Ye.
Acquisition of data: Hutson, Michaelson, Kuzel, Agarwal, Molina, Hsieh, Vaishampayan, Jain, Fishman.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Hutson, Bapat.
Critical revision of the manuscript for important intellectual content: All authors.
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***Data sharing statement*:** The study data will not be available for sharing at this time because the data are commercially confidential. However, Eisai Inc. will consider written requests to share the data on a case-by-case basis.

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.2021.03.015.

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Platinum Priority – Editorial

Referring to the article published on pp. 162–170 of this issue

Systemic Therapy for Advanced Non–clear-Cell Renal Cell Carcinoma: Slow but Definite Progress

Daniel M. Geynisman, Elizabeth R. Plimack *

Hematology/Oncology, Fox Chase Cancer Center, Temple Health, Philadelphia, PA, USA

Non–clear-cell renal cell carcinoma (nccRCC) accounts for approximately 20–25% of all RCC cases, comprises close to 15 different subtypes according to the 2016 World Health Organization classification [1], and displays immense morphologic, histologic, genomic, and clinical heterogeneity. The most common subtypes of nccRCC are papillary RCC (pRCC), further subclassified into types I and II, chromophobe RCC (chRCC), and unclassified RCC (uRCC). For those with advanced nccRCC, the prognosis and response to therapy have historically been inferior to clear cell RCC (ccRCC), in large part because of the lack of the *VHL* truncal mutation in nccRCC [2].

However, for the past 20 yr, treatment for nccRCC has nevertheless largely mirrored that for ccRCC owing to a lack of understanding of the biological drivers of the various nccRCC entities and few dedicated prospective trials, especially for any one particular nccRCC subtype. Trials continue to include multiple nccRCC subtypes, sometimes allowing ccRCC components, as well as various degrees of sacromatoid differentiation. Interpretation of any one trial is therefore often marred by ambiguity and definitive conclusions have been challenging to reach.

Sunitinib has been the de facto choice of agent on the basis of retrospective analysis, single-arm trials, and four moderate-sized ($\leq$108 patients) randomized phase 2 trials (ESPN, ASPEN, RECORD-3, and CESAR) that compared sunitinib to everolimus or temsirolimus. Although the overall response rate (ORR), median progression-free survival (mPFS), and median overall survival (mOS) varied between the trials, the general response rate for sunitinib has been $<$20% with PFS of 6–9 mo and mOS of approximately 15 mo; everolimus performed even worse. Multiple other single-arm prospective or retrospective studies showed a modest benefit with axitinib, pazopanib, cabozantinib, and, more recently, checkpoint inhibitors (CPIs) [3].

The advent of widespread genomic evaluation in oncology led to large-scale efforts to better delineate the mutational and metabolic landscape of nccRCC and revealed a diverse and distinct array of mutations in nccRCC subtypes [4,5]. For example, FH-deficient tumors and patients with hereditary leiomyomatosis and RCC (HLRCC) appear to respond well to VEGF/mTOR combinations (ORR 44%), but seem to respond very poorly to CPI (ORR 0%) [6]. Bevacizumab with erlotinib leads to an impressive ORR of 64% and mPFS of 21.1 mo for patients with HLRCC and should be considered as frontline therapy for this population [7]. RCCs with sarcomatoid and/or rhabdoid features are quite sensitive to CPI, alone or in combination with VEGF inhibition [8], and patients with *TSC1/2* or *MTOR* mutations occasionally exhibit a durable response to everolimus. *MET*-driven pRCC may be sensitive to selective MET inhibitors, but identification of tumors with true MET addiction remains challenging [9].

In this issue of *European Urology*, Hutson and colleagues [10] add to this body of work by presenting a prospective, single-arm, phase 2 trial of lenvatinib, a multikinase tyrosine kinase inhibitor (TKI), with everolimus for 31 patients with papillary (n = 20), chromophobe (n = 9), or unclassified RCC (n = 2). Most of the participants were classified as having intermediate or poor risk according to International Metastatic RCC Database Consortium criteria, and a minority had a prior nephrectomy. The key findings are an ORR of 26% confirmed on central radiology review, a disease control rate (DCR) of 84%, and mPFS of 9.2 mo

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* Corresponding author. Hematology/Oncology, Fox Chase Cancer Center, Temple Health, 333 Cottman Avenue, Philadelphia, PA 19111, USA. Tel. +1 215 7283889; Fax: +1 215 7283639. E-mail address: elizabeth.plimack@fccc.edu

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Table 1 – Select prospective trials in non–clear-cell RCC since 2015

	ASPEN [12]	Keynote 427 [8]	Len/Eve [10]	Bev/Eve [13,14]	Bev/Erlotinib [7]	PAPMET [11]
Patients	108	165	31	35	83 (42 HLRCC)	147 (44 Cabo)
Tx line	1st	1st	1st	1st	1st–*N*th	1st–2nd
Histologic subtypes	pRCC 65%	pRCC 72%	pRCC 65%	pRCC 14%	pRCC 100%	pRCC 100%
	chRCC 15%	chRCC 13%	chRCC 29%	chRCC 14%	HLRCC 52%	
	uRCC 20%	uRCC 16%	uRCC 6%	uRCC 66%	Sporadic 48%	
ORR	Sun 18%	26.7%	26%	29%	54.2%	Cabo 23%
	Eve 9%	pRCC 28.8%	pRCC 15%	RCC_{wpf} 35%	HLRCC 72.1%	Sun 4%
					Sporadic 35%	
mPFS	Sun 8.3 mo	4.2 mo	9.2 mo	11 mo	14.3 mo	Cabo 9.0 mo
	Eve 5.6 mo		IIR 5.6 mo	RCC_{wpf} 13.7 mo	HLRCC 21.1 mo	Sun 5.6 mo
					Sporadic 8.8 mo	
mOS	Sun 31.5 mo	28.9 mo	15.6 mo	18.5 mo	Not available	Cabo 20 mo
	Eve 13.2 mo					Sun 16.4 mo

Tx = therapy; RCC = renal cell carcinoma; pRCC = papillary RCC; chRCC = chromophobe RCC; uRCC = unclassified RCC; HLRCC = hereditary leiomyomatosis with RCC; ORR = overall response rate; mPFS = median progression-free survival; mOS = median overall survival; Len = lenvatinib; Sun = sunitinib; Eve = everolimus; Cabo = cabozantinib; Bev = bevacizumab; IIR = independent imaging review; wpf = with papillary features.

(although 5.2 mo by independent radiology review). Interestingly, the ORR for patients with chRCC was 44% with a DCR of 78%, a finding that requires prospective follow-up investigation as this may represent a promising combination for chRCC patients. Unfortunately, mOS was still only 15.6 mo, although it is unknown what subsequent therapy these patients were able to receive. The side-effects were consistent with the combination as approved for ccRCC and no new safety signals were uncovered. Although important limitations of this trial include a lack of central pathology review, no report of the degree of sarcomatoid features, and a relatively small sample size, the combination of lenvatinib and everolimus can now be considered an option for nccRCC patients, in particular those with chRCC.

It is also important to note two recent trials that have added data to support the use of cabozantinib and pembrolizumab for nccRCC patients. First, PAPMET was a randomized phase 2 trial of multiple TKIs for pRCC patients only that clearly showed the superiority of cabozantinib (starting dose 60 mg daily) over sunitinib, with PFS and ORR of 9.0 mo and 23% versus 5.6 mo and 4%, respectively (PFS: hazard ratio 0.6; $p = 0.019$) [11]. In addition, CABOSUN II (NCT03541902) is prospectively investigating cabozantinib versus sunitinib for a wide array of nccRCC patients. Second, Keynote 427 was a phase 2 prospective nonrandomized trial that showed the efficacy of pembrolizumab (ORR 26.7%) in pRCC/chRCC/uRCC [8]. In patients with a combined positive score $\geq$1, the ORR was 35.3% and the DCR was 50%. Both cabozantinib and pembrolizumab should be considered for nccRCC patients and adopted into practice. Table 1 lists a selection of key prospective trials in nccRCC since 2015.

Given that TKIs and CPIs both have some efficacy in nccRCC, combining the two classes is the reasonable next step. Important ongoing trials in this space include evaluations of cabozantinib with nivolumab (NCT03635892) and lenvatinib with pembrolizumab (NCT04267120); both combinations have already shown positive phase 3 results for ccRCC patients. Whether a TKI/everolimus/CPI triplet may be possible is unknown and the combination may be too toxic, but is worthy of investigation.

We recommend considering the following general principles for any patient with nccRCC.

(1) Expert genitourinary pathologic review should be attempted as it may help to correctly characterize the subtype and thus help to fine-tune treatment decisions.
(2) Genomic analysis should be considered for select patients, using the most recent specimen and ideally a metastatic lesion, as this may help to identify targets such as ALK, TSC1, TSC2, MTOR, or MET that can guide therapy and clinical trial participation.
(3) Clinical trials remain the preferred treatment option.
(4) Patients with nccRCC harboring sarcomatoid and/or rhabdoid differentiation should be treated with a CPI combination in the frontline setting.
(5) Genetic evaluations should be considered for those who are young, exhibit syndromic features, or have a family history consistent with a genetic syndrome such as HLRCC.
(6) Cabozantinib, pembrolizumab, bevacizumab/erlotinib, bevacizumab/everolimus, and lenvatinib/everolimus are all reasonable frontline options depending on a particular clinical scenario. How to sequence these agents is unknown.

There has undoubtedly been progress in the evaluation and management of nccRCC, but much remains to be done. We expect that the next decade will lead to more precise molecular classification and biomarker-directed management of this rare and diverse group of patients.

Conflicts of interest: Elizabeth R. Plimack acts in a consulting or advisory role for BMS, Genentech, Janssen, Merck, Flatiron, Seattle Genetics, Pfizer, AstraZeneca, Infity Pharma, and MEI Pharma; has received institutional research funding from BMS, AstraZeneca, Pfizer, Merck, Astellas, and Genentech; and has an interest in US patent 14/588

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Platinum Priority – Review – Benign Prostatic Hyperplasia – Editor's Choice

Editorial by Ruben Blachman-Braun, Jesse Ory, Hemendra N. Shah and Ranjith Ramasamy on pp. 188–189 of this issue

Erectile Function Following Surgery for Benign Prostatic Obstruction: A Systematic Review and Network Meta-analysis of Randomised Controlled Trials

Alexander Light[a], *Dost Jabarkhyl*[b], *Peter Gilling*[c], *Gincy George*[d], *Mieke Van Hemelrijck*[d], *Ben Challacombe*[e], *Sachin Malde*[e], *Rick Popert*[e], *Prokar Dasgupta*[b,e,*], *Oussama Elhage*[b,e]

[a] *Department of Surgery, University of Cambridge, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK;* [b] *Faculty of Life Sciences and Medicine, King's College London, London, UK;* [c] *Department of Urology, Tauranga Hospital, Bay of Plenty District Health Board, Tauranga, New Zealand;* [d] *Translational Oncology & Urology Research, School of Cancer and Pharmaceutical Sciences, King's College London, London, UK;* [e] *Department of Urology, Guy's and St Thomas' NHS Foundation Trust, London, UK*

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Abstract

Context: Benign prostatic obstruction (BPO) is associated with sexual dysfunction. Furthermore, numerous BPO interventions may themselves impact sexual function.
Objective: To perform a systematic review with network meta-analysis to evaluate how BPO interventions affect erectile function.
Evidence acquisition: Three databases were searched for randomised controlled trials (RCTs) comparing surgical interventions for BPO. The primary outcome was postoperative International Index of Erectile Function-5 (IIEF-5) score at ten time points up to 72 mo. A random-effects Bayesian network meta-analysis with meta-regression was performed. In comparison to monopolar transurethral resection (mTURP), the mean difference (MD) with 95% credible interval (CrI) and rank probability (rank *p*) were calculated for interventions. The mean baseline score was studied in meta-regression. τ^2 values were used to quantify heterogeneity.
Evidence synthesis: A total of 48 papers (33 RCTs, 5159 patients, 16 interventions) were included. Prostatic urethral lift (PUL) ranked highest at 1 mo (MD 3.88, 95% CrI −0.47 to 8.25; rank $p = 0.742$), 6 mo (MD 2.43, 95% CrI −0.72 to 5.62; rank $p = 0.581$), 12 mo (MD 2.94, 95% CrI −0.26 to 6.12, rank $p = 0.782$), and 24 mo (MD 3.63, 95% CrI 0.14 to 7.11; rank $p = 0.948$), at which point statistical significance was reached. At time points up to 60 mo, there were no statistically significant comparisons for other interventions. Analyses were not possible at 18, 48, or 72 mo. β did not reach statistical significance in meta-regression. τ^2 was highest at 1 mo (0.56) and 60 mo (0.55).
Conclusions: PUL ranked highly and resulted in erectile function improvement at 24 mo compared to mTURP, but direct evidence is lacking. We did not observe significant differences in erectile function following other interventions up to 60 mo. Owing to heterogeneity, our conclusions are weakest at 1 and 60 mo. Further RCTs comparing sexual function outcomes are recommended, such as PUL versus holmium laser or bipolar enucleation.
Patient summary: Different surgical treatments can be used to treat benign enlargement of the prostate causing urinary problems. We compared the effects of various

* Corresponding author. Department of Urology, Guys Hospital, Great Maze Pond, London SE1 9RT, UK. Tel. +44 207 1887188.
E-mail address: prokar.dasgupta@kcl.ac.uk (P. Dasgupta).

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treatments on erectile function at time points up to 5 years after surgery. Compared to surgical removal of some of the prostate gland (transurethral resection of the prostate, TURP), a technique called prostatic urethral lift resulted in better erectile function scores at 24 months. However, other treatments did not differ in their effect on erectile function.

1. Introduction

Benign prostatic obstruction (BPO) causes lower urinary tract symptoms (LUTS), which detrimentally affect quality of life [1,2]. However, BPO and sexual dysfunction have a complex relationship, with strong associations between sexual dysfunction and LUTS independent of sexual dysfunction risk factors such as age and diabetes [3–9]. LUTS severity is also strongly correlated to erectile dysfunction severity [4]. Plausible mechanisms include reduced production of nitric oxide by prostatic and penile smooth muscle, autonomic overactivity, upregulated Rho-kinase activity, and pelvic atherosclerosis [10].

Surgical intervention for BPO is reserved for indications such as failed medical therapy, refractory urinary retention, and renal failure. Some patients also prefer a more definitive alternative to medication. The traditional standard has been monopolar transurethral resection of the prostate (mTURP), although there is now an armamentarium of new interventions, such as prostatic urethral lift (PUL) and prostatic arterial embolisation (PAE) [11]. An important consideration for any prostatic intervention, however, is the possible worsening of sexual function due to damage to cavernosal nerves and related structures. Though, despite risking sexual dysfunction, it is unclear if successful surgery could actually improve sexual function. Furthermore, to better rank the multitude of available treatments, it is important to consider patient-centred outcomes such as sexual function when comparing treatments.

Network meta-analysis facilitates both direct and indirect comparisons and ranking of treatments. We performed a systematic review with network meta-analysis of randomised-controlled trial (RCT) data to compare the effect of surgical interventions on sexual function in patients with BPO.

2. Evidence acquisition

2.1. Protocol

The protocol for this study is registered with PROSPERO (CRD42019155506).

2.2. Search strategy

MEDLINE, Embase, and Web of Science databases were searched on October 13, 2019 for articles since database inception. The Supplementary material details our search string. We also consulted experts and references from relevant reviews for additional articles. Where a relevant meeting abstract was identified, we manually searched for a corresponding full-text article. Two authors screened the search results.

2.3. Eligibility criteria

Table 1 outlines the eligibility criteria. If an article presented insufficient data, the corresponding author was contacted. If no response was received or data were unavailable, the paper was excluded.

2.4. Outcomes

Questionnaires under study were the International Index of Erectile Function-5 (IIEF-5), the full IIEF instrument, Men's Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD), MSHQ-Bother, and Brief Sexual Function

Table 1 – Inclusion and exclusion criteria for the studies identified

Include	Exclude
RCTs	Men with concomitant or previous prostate cancer
Comparison of two distinct BPO surgical interventions (can include sham)	Studies comparing variations of the same intervention without comparison to another distinct intervention
Crossover RCTs only if the control arm was sham, and only until the crossover point	Observational studies
Use of IIEF-5, full IIEF, MSHQ-EjD, MSHQ-Bother, or BSFI	Review articles
Primary treatment	Letters
Repeat treatment	Commentaries
	Meeting abstracts
	Animal studies
	Simulation or training studies
	Articles not in English
	Insufficient data despite contacting the authors

BPO = benign prostatic obstruction; BSFI = Brief Sexual Function Inventory; EjD = Ejaculatory Dysfunction domain; IIEF = International Index of Erectile Function; MSHQ = Men's Sexual Health Questionnaire; RCT = randomised controlled trial.

Inventory (BSFI). Postoperative questionnaire scores, including those for individual domains, were compared. The primary outcome was the IIEF-5 score, reflecting erectile function, as we anticipated that this questionnaire would be most widely used. Scores were considered at 1, 3, 6, 12, 18, 24, 36, 48, 60, and 72 mo of follow-up.

2.5. Data extraction

Shortlisted articles were assessed against eligibility criteria by two authors, and data were extracted from eligible articles into a prespecified spreadsheet. Any dispute was settled via consensus.

2.6. Risk-of-bias assessment

The Cochrane Risk of Bias 2.0 tool was used to assess methodological quality [12]. Publication bias was assessed via visual examination of comparison-adjusted funnel plots.

2.7. Statistical analysis

Pairwise meta-analysis using a random-effects model was used first to compare postoperative scores. The mean difference (MD) and 95% confidence interval were calculated.

Bayesian network-meta analysis with meta-regression was performed at each time point using the *gemtc* package in R and at https://gemtc.drugis.org/. The MD and 95% credible interval (CrI) and rank probability (rank p) were calculated. mTURP was used as the primary reference given its widespread use and consideration as the traditional standard. However, post hoc we chose other interventions as the reference to facilitate more global assessment. With a lack of robust understanding regarding postoperative sexual dysfunction, we used uninformative prior distributions as automatically chosen by *gemtc* to achieve an objective, data-driven analysis. Bayesian network meta-analysis with uninformative prior distributions is recommended by the UK National Institute for Health and Care Excellence (NICE), as this facilitates probabilistic treatment ranking to improve decision-making [13]. For Markov chain Monte Carlo simulation, settings of 5000 burn-ins, 100 000 inference iterations, and a thinning factor of 10 were used. A random-effects model was used in anticipation of inter-study heterogeneity, although post hoc fixed-effects sensitivity analyses were also performed. Model fits were compared using the Bayesian deviance information criterion (DIC), with differences of 2–5 considered significant [14]. For calculation of β in meta-regression, the baseline questionnaire score was the covariate chosen.

Heterogeneity was assessed using the τ^2 statistic, the between-study variance in random-effects models. Prediction intervals based on τ were then calculated for IIEF-5 analyses to aid clinical interpretation of this heterogeneity [15]. The prediction interval gives the range within which the effect size of a future study would lie, if that study were to be selected at random from the same population of studies included within this network meta-analysis [16]. To investigate heterogeneity, we performed subgroup analyses, meta-regression analyses, and a fixed-effects sensitivity analysis as detailed below. Node-splitting models were used to evaluate consistency between direct and indirect comparisons.

2.8. Sensitivity and subgroup analyses

First, we separated studies by mean baseline IIEF-5 score as ≤21 versus >21, and then ≤16 versus >16. Second, interventions were grouped to increase statistical power: mTURP, bipolar TURP (bTURP), enucleation, vaporisation, and simple prostatectomy, with the other treatments remaining individual. Third, we used mean prostate volume as the covariate in meta-regression. A specific gravity of 1.05 g/cm^3 was used to convert prostate weight to volume where only weights were presented. With this, we also grouped studies by mean prostate volume: ≤70 ml versus >70 ml. Post hoc, we applied ≤60 ml versus >60 ml, and then ≤80 ml versus >80 ml as cutoffs to reflect discrepancies in defining a large prostate. Fourth, we used mean age as a covariate in meta-regression, and then performed subgroup analysis using age ≤65 yr versus >65 yr. Finally, we conducted fixed effects sensitivity analyses post hoc to characterise the impact of choosing a random-effects model.

2.9. Quality-of-evidence assessment

The quality of treatment effects was assessed using the GRADE methodology [17]. Quality assessments ranged from grade A (high) to grade D (very low).

3. Evidence synthesis

3.1. Study characteristics

From 4606 search results, 48 papers representing 33 RCTs were included (Fig. 1) [18–65]. These encompassed 16 interventions and 5159 patients (Table 2). On request, the authors of the WATER trial provided additional data [35–37]. A total of 26 trials used the IIEF-5 [18–23,25–30,35–42,47,49–65]. Nine used the full IIEF instrument [24,31–37,43–46,48], of which six provided individual domain results [24,32,33,43,44,48]. Three trials used the MSHQ-EjD and MSHQ Bother instruments [35–37,44–46,53–58]. None used the BSFI.

3.2. IIEF-5 results

3.2.1. Overview

Figure 2 shows network plots for IIEF-5 results. Thirteen interventions were compared: mTURP, bTURP, photoselective vaporisation (PVP), holmium laser enucleation (HoLEP), diode laser enucleation (diode LEP), thulium laser enucleation (ThuLEP), bipolar enucleation (bEP), open prostatectomy (OP), laparoscopic simple prostatectomy (LSP), PUL, PAE, Aquablation, and sham.

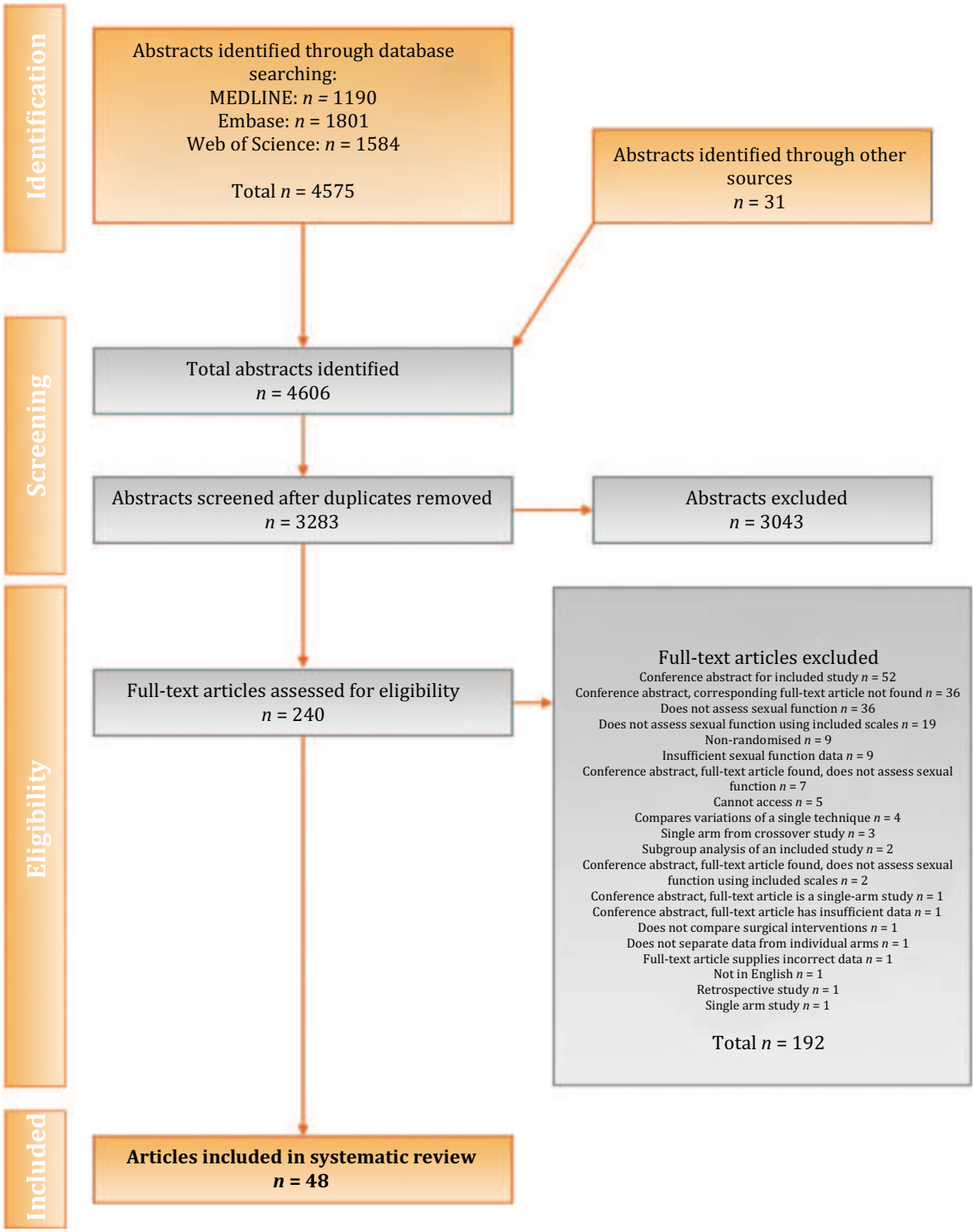

Fig. 1 – PRISMA flow diagram showing the search and screening process to identify eligible articles. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Sufficient data were available for network meta-analysis at 1, 3, 6, 12, 24, 36, and 60 mo. Figure 3 shows forest plots for each time point and Table 3 lists the rank probabilities. Supporting analyses are shown in Supplementary Table 1A–C and Supplementary Figure 1A–H.

3.2.2. Results at 1, 3, and 6 mo

At 1, 3, and 6 mo, eight, 12, and 11 interventions were compared, respectively [18–20,30,35–42,47,49,50,52–65]. PUL ranked highest at 1 mo (MD 3.88, 95% CrI −0.47 to 8.25; rank p = 0.742) and 6 mo (MD 2.43, 95% CrI −0.72 to

Table 2 – Characteristics of the studies included in the review

Study	Study period	Type	Location	Comparisons	Participants	Age (yr)	Mean prostate volume or weight	Follow-up (mo)	Sexual function questionnaires assessed
[18]	NR	SC	Switzerland	PAE mTURP	51 52	65.7 (9.3) 66.1 (9.8)	52.8 (32.0) ml 56.5 (31.1) ml	3	IIEF-5
[19,20]	March 2005 to April 2006	SC	Greece	PVP (80 W) OP	65 60	74 (67–80) 67.5 (65–74)	93 (85–100) ml 96 (86–100) ml	18	IIEF-5
[21–23] (GOLIATH)	April 2011 to September 2012	MC	Europe	mTURP PVP (180 W)	142 139	65.4 (6.6) 65.9 (6.8)	46.2 (19.1) ml 48.6 (19.2) ml	23.2 (3.6) 23.3 (3.1)	IIEF-5
[24]	January 2002 to January 2003	MC	Italy	HoLEP mTURP	60 60	65.25 (6.9) 64.18 (7.2)	73.3 (31.7) g 58.2 (21.48) g	24	Full IIEF, domains available
[25]	November 2010 to December 2012	SC	Brazil	mTURP PAE	15 15	66.4 (5.6) 63.5 (8.7)	56.6 (21.5) ml 63.0 (17.8) ml	12	IIEF-5
[26,27]	April 2005 to August 2007	SC	China	bTURP mTURP	50 50	69.7 (7.6) 71.2 (6.3)	60.2 (18.7) ml 59.1 (17.3) ml	24	IIEF-5
[28,29]	August 2008 to February 2010	SC	China	HoLEP bTURP	140 140	72.11 (7.8) 73.48 (8.8)	56.70 (28.41) ml 60.31 (22.41) ml	72	IIEF-5
[30]	January 2004 to June 2007	SC	China	bEP OP	80 80	64.7 (3.7) 63.7 (4.5)	110 (102–130) g 114.5 (104–128) g	72	IIEF-5
[31]	November 2013 to June 2015		Turkey	bTURP mTURP	59 59	65.00 (9.0) 66.87 (10.10)	71.80 (12.93) ml 73.90 (14.13) ml	6	Full IIEF
[32]	January 2013 to December 2014	SC	Egypt	mTURP bTURP	149 145	64 (7.7) 62 (6.3)	63 (23) ml 68 (22) ml	12	Full IIEF, domains available
[33]	March 2005 to April 2007	SC	Canada	PVP HoLEP	52 57	71.6 (10.3) 72.7 (10.3)	37.3 (13.6) ml 33.1 (14.5) ml	36	Full IIEF, domains available
[34]	October 2014 to November 2015	SC	Egypt	PVP (180 W) bTUVP	58 59	64.5 (7.0) 62.8 (6.7)	59.3 (13.0) ml 55.9 (12.4) ml	24	Full IIEF
[35–37] (WATER) [a]	October 2015 to December 2016	MC	International	Aquablation mTURP	117 67	66.0 (7.3) 65.8 (7.2)	54.1 (16.2) ml 51.8 (13.8) ml	24	IIEF-5, full IIEF, MSHQ-EjD, MSHQ-Bother
[38]	January 2005 to March 2006	SC	Turkey	mTURP PVP (80 W)	37 39	68.3 (6.7) 69.2 (7.1)	88.0 (9.2) ml 86.1 (8.8) ml	6	IIEF-5
[39]	August 2012 to July 2015	SC	India	mTURP HoLEP	72 72	66.78 (7.81) 67.70 (7.44)	74.5 (12.56) ml 75.6 (12.84) ml	24	IIEF-5
[40,41]	March 2011 to February 2012	SC	India	mTURP bTURPP VP (120 W)	60 57 58	63.68 (6.57) 62.31 (6.36) 64.58 (6.64)	52.50 (15.93) ml 50.26 (16.50) ml 52.79 (16.13) ml	36	IIEF-5
[42]	May 2008 to May 2011	SC	China	mTURP bTURP	350 340	67.15 (9.73) 66.32 (8.25)	67.43 (13.72) ml 65.60 (13.70) ml	60	IIEF-5
[43]	June 2006 to July 2009	MC	Europe	mTURP bTURP	149 146	67.9 (8.3) 69.0 (8.2)	63.3 (29.1) ml 64.0 (27.9) ml	12	Full IIEF, domains available
[44–46]	September 2013 to August 2014	MC	USA	Rezūm Sham	136 61	63.0 (7.1) 62.9 (7.0)	45.8 (13.0) ml 44.5 (13.3) ml	3 (COP) (48 in total)	Full IIEF, domains available; MSHQ-EjD, MSHQ-Bother
[47]	February 2009 to August 2009	SC	India	PVP (80 W) mTURP	60 57	66.68 (8.62) 65.74 (9.09)	44.77 (14.09) ml 49.02 (15.93) ml	12	IIEF-5
[48]	January 2002 to October 2002	MC	Italy	HoLEP mTURP	52 48	65.14 64.50	70.3 (36.7) ml 56.2 (19.4) ml	12	Full IIEF, domains available
[49]	March 2003 to December 2004	SC	Italy	HoLEP OP	41 39	66.26 (6.55) 67.27 (6.72)	113.27 (35.33) g 124.21 (38.52) g	24	IIEF-5

Table 2 (*Continued*)

Study	Study period	Type	Location	Comparisons	Participants	Age (yr)	Mean prostate volume or weight	Follow-up (mo)	Sexual function questionnaires assessed
[50]	April 2009 to June 2009	SC	Brazil	PVP (120 W)	10	66.4 (52–76)	47 (30–60) ml	24	IIEF-5
				mTURP	10	63.5 (56–78)	43.4 (30–58) ml		
[51]	January 2010 to March 2012	SC	India	mTURP	57	65.3 (7.86)	69.6 (16.3) ml	48	IIEF-5
				PVP (120 W)	60	63.6 (8.12)	70.3 (15.5) ml		
[52]	July 2007 to September 2011	SC	China	bEP	43	66.6 (7.5)	116.2 (32.4) ml	12	IIEF-5
				OP	40	65.8 (6.9)	110.2 (32.1) ml		
[53–56] (L.I.F.T.)	February 2011 to December 2011	MC	International	PUL	140	67 (8.6)	44.5 (12.4) ml	3 (COP)	IIEF-5, MSHQ-EjD,
				Sham	66	65 (8.0)	40.9 (10.8) ml	(60 in total)	MSHQ-Bother
[57,58] (BPH6)	February 2012 to October 2013	MC	Europe	PUL	45	63 (6.8)	38 (12) ml	24	IIEF-5, MSHQ-EjD,
				mTURP	35	65 (6.4)	41 (13) ml		MSHQ-Bother
[59]	January 2010 to November 2011	SC	China	ThuLEP	45	69.89 (8.18)	112.86 (28.36) ml	18	IIEF-5
				bTURP	45	69.02 (7.05)	115.04 (39.45) ml		
[60]	January 2013 to June 2014	SC	China	bEP	40	73.6 (6.2)	93.3 (18.5) ml	12	IIEF-5
				Diode LEP	40	75.4 (8.4)	98.6 (21.6) ml		
[61]	November 2004 to December 2005	SC	China	ThuLEP	52	68.9 (7.7)	93.1 (32.1) ml	12	IIEF-5
				mTURP	48	69.3 (7.3)	85.0 (36.7) ml		
[62]	June 2008 to April 2010	SC	China	LSP	36	71.7 (9.3)	93.3 (14.8) ml	36	IIEF-5
				bTURP	54	72.1 (8.8)	96.6 (12.1) ml		
[63]	January 2004 to December 2006	SC	China	bEP	102	67.3 (6.6)	69.2 (13.5) ml	36	IIEF-5
				mTURP	102	67.8 (6.4)	67.5 (11.8) ml		
[64]	June 2004 to December 2006	SC	China	bEP	40	64.1 (4.8)	113.8 (32.0) ml	60	IIEF-5
				bTURP	40	64.8 (3.9)	109.4 (32.4) ml		
[65]	NR	MC	China	Diode LEP	57	67.3 (7.7)	59.5 (28.8) ml	12	IIEF-5
				bEP	57	69.4 (7.5)	63.4 (36.4) ml		

NR = not reported; SC = single-centre study; MC = multicentre study; TURP = transurethral resection of the prostate; mTURP = monopolar TURP; bTURP = bipolar TURP; PUL = prostatic urethral lift; PVP = photoselective vaporisation of the prostate; bTUVP = bipolar transurethral vaporisation of the prostate; OP = open prostatectomy; bEP = bipolar enucleation of the prostate; HoLEP = holmium laser enucleation of the prostate; PAE = prostatic arterial embolisation; ThuLEP = thulium LEP; LSP = laparoscopic simple prostatectomy; COP = crossover point.

[a] The authors of the WATER trial provided additional data on request.

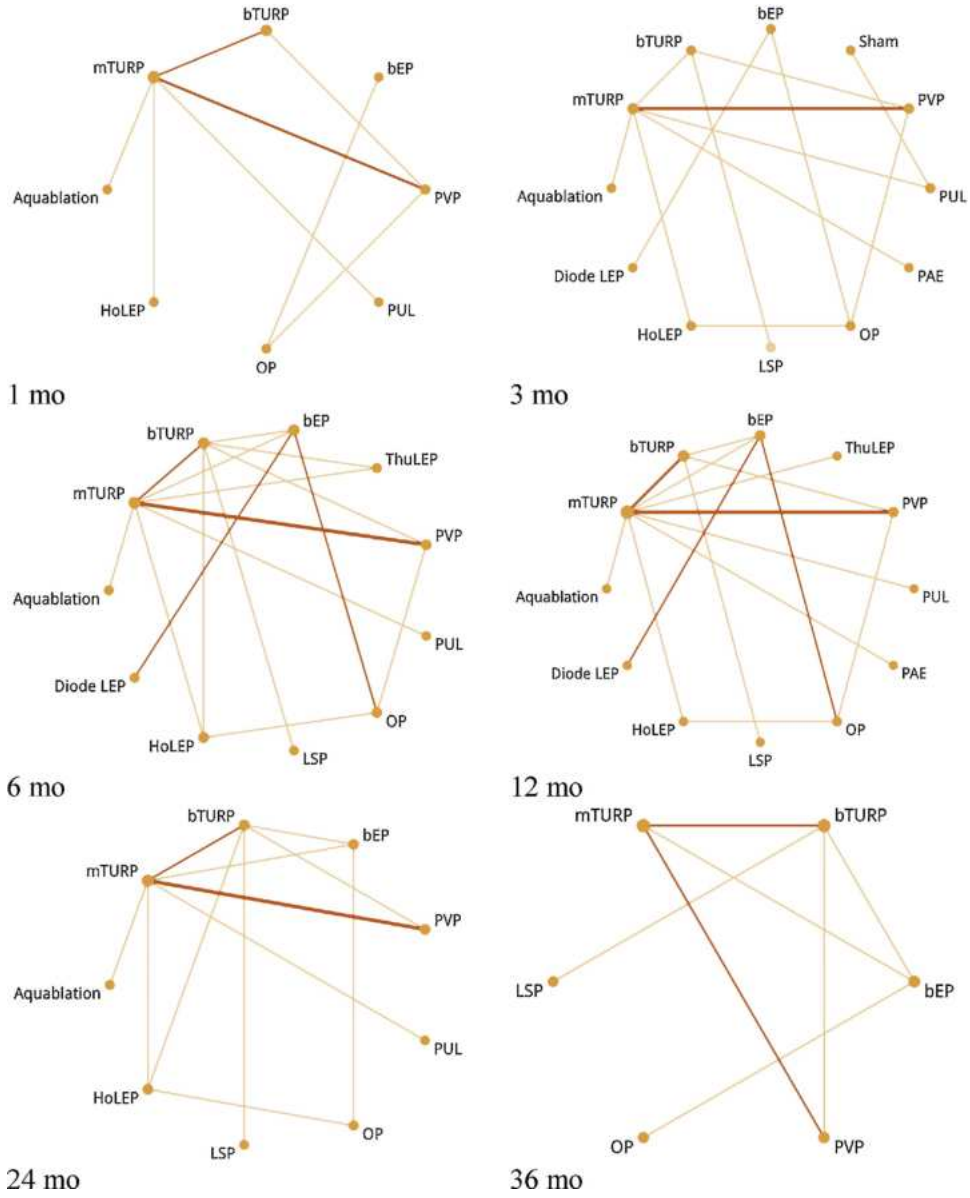

Fig. 2 – Network plots comparing International Index of Erectile Function-5 scores at 1, 3, 6, 12, 24, and 36 mo after 13 different interventions: monopolar transurethral resection of the prostate (mTURP), bipolar TURP (bTURP), photoselective vaporisation of the prostate (PVP), holmium laser enucleation of the prostate (HoLEP), diode LEP, thulium LEP (ThuLEP), bipolar enucleation of the prostate (bEP), open prostatectomy (OP), laparoscopic simple prostatectomy (LSP), prostatic urethral lift (PUL), prostatic arterial embolisation (PAE), Aquablation, and sham. At 60 mo (network plot not shown), there were four interventions in single study comparisons: mTURP, bTURP, bEP, and OP.

5.62; rank p = 0.581). At 3 mo, sham intervention ranked highest (MD 3.19, 95% CrI −1.52 to 7.90; rank p = 0.490), with PAE second (MD 3.00, 95% CrI −0.002 to 5.96; rank p = 0.290). For other comparisons, there were no significant differences in scores, including when using non-mTURP interventions as the comparator (Supplementary Table 1C, G,K). β did not reach statistical significance (1 mo: −1.15, 95% CrI −4.21 to 2.16; 3 mo: 0.20, 95% CrI −1.83 to 2.10; 6 mo: −0.39, 95% CrI −1.82 to 0.71).

3.2.3. *Results at 12 mo*

Twelve interventions were compared [19–25,30–37,39–42,49–52,57,58,60–65]. PUL ranked highest (MD 2.94, 95% CrI −0.26 to 6.12; rank p = 0.782). For other comparisons, there were no significant differences in scores. When non-mTURP interventions were used as the comparator, PUL resulted in significantly higher IIEF-5 scores compared to LSP, OP, PAE, and bTURP (Supplementary Table 1O). OP also resulted in a significantly lower score compared to HoLEP. β did not reach statistical significance (0.38, 95% CrI −0.83 to 1.75).

3.2.4. *Results at 24 mo*

Nine interventions were compared [21–23,30,35–37,39–41,49–51,57,58,62–64]. At 24 mo, PUL ranked highest and resulted in significantly higher IIEF-5 scores (MD 3.63, 95%

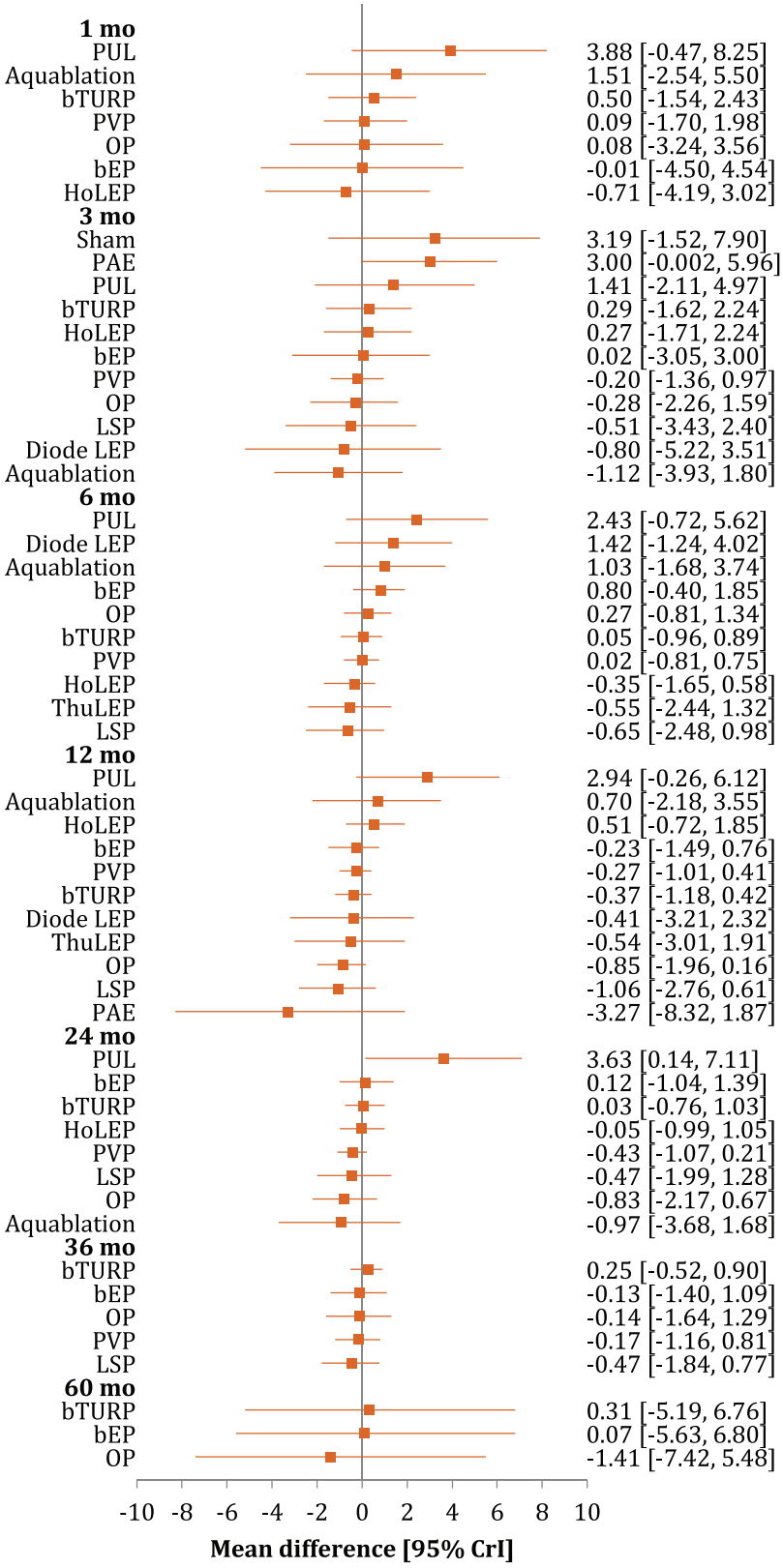

Fig. 3 – Forest plots of International Index of Erectile Function-5 (IIEF-5) network meta-analysis for comparison of mTURP versus other interventions at each follow-up time, using baseline IIEF-5 score as the covariate in meta-regression. TURP = transurethral resection of the prostate; mTURP = monopolar TURP; bTURP = bipolar TURP; PUL = prostatic urethral lift; PVP = photoselective vaporisation of the prostate; OP = open prostatectomy; bEP = bipolar enucleation of the prostate; HoLEP = holmium laser enucleation of the prostate; PAE = prostatic arterial embolisation; ThuLEP = thulium LEP; LSP = laparoscopic simple prostatectomy; CrI = credible interval.

Table 3 – Modalities with the highest rank probability (*p*) at each follow-up time point in network meta-analysis for postoperative IIEF-5 scores

Time point	Rank probability for postoperative IIEF-5 score											
(ITVs)	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
1 mo (8)	PUL	Aquablation	bTURP	PVP	PVP	mTURP	mTURP	HoLEP				
	p = 0.742	p = 0.408	p = 0.302	p = 0.198	p = 0.241	p = 0.244	p = 0.215	p = 0.475				
3 mo (12)	Sham	PAE	PUL	bTURP	bTURP	mTURP	mTURP	PVP	OP	OP	Aquablation	Aquablation
	p = 0.490	p = 0.290	p = 0.323	p = 0.188	p = 0.184	p = 0.198	p = 0.212	p = 0.192	p = 0.183	p = 0.165	p = 0.196	p = 0.362
6 mo (11)	PUL	Diode LEP	bEP	bEP	OP	bTURP	mTURP	mTURP	HoLEP	HoLEP	LSP	
	p = 0.581	p = 0.320	p = 0.355	p = 0.287	p = 0.245	p = 0.190	p = 0.228	p = 0.204	p = 0.235	p = 0.236	p = 0.360	
12 mo (12)	PUL	Aquablation	HoLEP	mTURP	mTURP	mTURP	bTURP	bTURP	OP	OP	LSP	PAE
	p = 0.782	p = 0.327	p = 0.314	p = 0.245	p = 0.280	p = 0.199	p = 0.210	p = 0.209	p = 0.243	p = 0.278	p = 0.296	p = 0.709
24 mo (9)	PUL	bEP	bTURP	bTURP	bTURP	PVP	PVP	OP	Aquablation			
	p = 0.948	p = 0.328	p = 0.235	p = 0.253	p = 0.204	p = 0.213	p = 0.282	p = 0.329	p = 0.464			
36 mo (6)	bTURP	bTURP	mTURP	mTURP	bEP	LSP						
	p = 0.429	p = 0.254	p = 0.244	p = 0.228	p = 0.236	p = 0.467						
60 mo (4)	mTURP	bTURP	bEP	OP								
	p = 0.349	p = 0.434	p = 0.378	p = 0.701								

IIEF-5 = International Index for Erectile Function-5; ITVs = number of interventions; TURP = transurethral resection of the prostate; mTURP = monopolar TURP; bTURP = bipolar TURP; PUL = prostatic urethral lift; PVP = photoselective vaporisation of the prostate; OP = open prostatectomy; bEP = bipolar enucleation of the prostate; HoLEP = holmium laser enucleation of the prostate; PAE = prostatic arterial embolisation; LSP = laparoscopic simple prostatectomy.

CrI 0.14 to 7.11; rank p = 0.948). For other comparisons, there were no significant differences in scores. When non-mTURP interventions were used as the comparator, PUL also resulted in significantly higher scores compared to Aquablation, HoLEP, PVP, LSP, and OP (Supplementary Table 1S). β did not reach statistical significance (−0.40, 95% CrI −1.26 to 0.64).

3.2.5. *Results at 36 mo*

Six interventions were studied [30,40–42,51,62–64]. PUL data were unavailable beyond 24 mo. bTURP ranked highest (MD 0.25, 95% CrI −0.52 to 0.90; rank p = 0.429). For all comparisons, there were no significant differences in scores, including when using non-mTURP interventions as the comparator (Supplementary Table 1W). β did not reach statistical significance (0.07, 95% CrI −1.33 to 1.56).

3.2.6. *Results at 60 mo*

Four interventions were analysed [30,42,64]. mTURP ranked highest (rank p = 0.349) but there were no significant differences in scores, including when using non-mTURP interventions as the comparator (Supplementary Table 1AA). β did not reach statistical significance (0.06, 95% CrI −10.01 to 12.10).

3.3. *Results for the full IIEF instrument*

Owing to a paucity of data, network meta-analyses of full IIEF data, as well as domain data, were only possible at 6 and 12 mo (Supplementary Tables 2C and 3G).

3.4. *MSHQ-EjD and MSHQ-Bother*

Network meta-analyses were possible at 1, 3, 6, 12, and 24 mo for Aquablation, mTURP, Rezūm, and sham interventions in four RCTs (Supplementary Tables 4B and 5B). For the MSHQ-EjD, PUL ranked highest at 1, 6, 12, and 24 mo, although the results were imprecise. Regarding the MSHQ-Bother, mTURP ranked highest at all time points. No comparison reached statistical significance.

3.5. *Sensitivity and subgroup analyses*

Further analyses were only performed with IIEF-5 data given the limited data for other questionnaires. When comparing studies with mean baseline scores >16 and ≤21, no comparison, including PUL, reached statistical significance (Supplementary Tables 6A and 8A). Comparison of studies with mean baseline scores ≤16 was possible with a few studies at 3, 12, and 24 mo, which did not include PUL data (Supplementary Table 7A). Incomplete networks prevented comparison of studies with mean baseline scores >21.

On grouping of modalities, PAE resulted in a significantly higher score at 3 mo (MD 2.90, 95% CrI 0.63 to 5.22) and PUL at 24 mo (MD 3.64, 95% CrI 0.15 to 7.01) (Supplementary Table 9A). For other comparisons, there were no significant differences in scores.

When performing meta-regression using mean prostate volume, results were comparable to our primary analysis,

with the result for PUL at 24 mo reaching statistical significance (Supplementary Table 10A). β did not reach statistical significance at any time point. On comparing studies with mean prostate volume ≤70 ml and ≤80 ml, the result for PUL at 24 mo reached statistical significance (Supplementary Tables 11A and 15A). When grouping studies with mean prostate volume ≤60 ml, PUL did not yield a significant result at 24 mo (Supplementary Table 13A). All other comparisons did not reach statistical significance.

For trials with mean prostate volume >60 ml, >70 ml, and >80 ml, no comparison reached statistical significance (Supplementary Tables 12A, 14A, and 16A). Notably, no PUL data were available for any of these analyses.

When performing meta-regression using mean age, PAE resulted in a significantly higher score at 3 mo (MD 2.83, 95% CrI 0.04 to 5.59), and OP a significantly lower score at 12 mo (MD −0.97, 95% CrI −1.92 to −0.04) when compared to mTURP (Supplementary Table 17A). By contrast, PUL did not result in a difference in score at 24 mo. All other comparisons and β values did not reach statistical significance at any time point. On comparing studies with mean age ≤65 yr versus >65 yr, no comparison reached statistical significance (Supplementary Tables 18A and 19A).

3.6. Heterogeneity and inconsistency

For IIEF-5 analyses, between-study heterogeneity was greatest at 1 mo (τ^2 = 0.56) and 60 mo (τ^2 = 0.55). At other time points, heterogeneity was observed but to a lesser degree (3 mo: τ^2 = 0.28; 6 mo: τ^2 = 0.18; 12 mo: τ^2 = 0.20; 24 mo: τ^2 = 0.09; 36 mo: τ^2 = 0.06). Prediction intervals are shown in Supplementary Figure 1I–O.

At 1 mo in subgroup analysis, τ^2 decreased to 0.05 with mean prostate volume ≤60 ml, and increased to 2.38 for studies with mean prostate volume >60 ml, suggesting that interstudy variability in prostate volume could explain heterogeneity at this time point (Supplementary Tables 13A and 14A). However, in meta-regression, neither prostate volume, baseline questionnaire score, nor age significantly affected the summary estimates (Supplementary Tables 10A and 17A). τ^2 did not decrease in other subgroup analyses (Supplementary Tables 6A, 8A, 11A, 15A, 18A, and 19A).

Given the paucity of studies with 60-mo follow-up, subgroup analyses were only possible using mean preoperative IIFE-5 scores ≤21, for which τ^2 decreased to 0.02 (Supplementary Table 6A). Differences in baseline questionnaire score may therefore have contributed to heterogeneity at this time point.

In fixed-effects analyses, the 95% CrI narrowed and some further comparisons became significant. These were as follows: PUL at 1 mo (MD 3.71, 95% CrI 0.19 to 7.22), PVP at 1 mo (MD −0.58, 95% CrI −1.03 to −0.13), PAE at 3 mo (MD 2.90, 95% CrI 0.76 to 5.03), and PVP at 24 mo (MD −0.43, 95% CrI −0.82 to −0.04; Supplementary Fig. 1H). Differences in DIC were nonsignificant [14]. For fixed-effects versus random-effects models, DIC values were 37.2 versus 37.6 at 1 mo, 54.6 versus 56.0 at 3 mo, 74.4 versus 74.7 at 6 mo, 76.6 versus 76.4 at 12 mo, 50.6 versus 51.7 at 24 mo, 25.9 versus 26.8 at 36 mo, and 12.0 versus 12.0 at 60 mo.

In general, high interstudy heterogeneity was observed at each time point for other questionnaires. However, further investigation was not undertaken owing to limited data (Supplementary Tables 2C, 3G, 4B, and 5B).

Inconsistency was observed at 6-mo IIEF-5 analyses between HoLEP and OP (p = 0.04) (Table S1M). No other inconsistency was noted (Supplementary material).

3.7. Risk of bias

Overall, 15 studies had low risk of bias, 16 had some concerns, and three had high risk of bias (Supplementary Table 20). Publication bias was minimal according to comparison-adjusted funnel plots (Supplementary material).

3.8. Quality of evidence

In IIEF-5 analyses, of 265 summary estimates, 70 (26.4%) were grade A, 155 (58.5%) grade B, 39 (14.7%) grade C, and one (0.4%) grade D (Supplementary material).

3.9. Discussion

3.9.1. Summary

Our primary analysis focused on erectile function over 60-mo follow-up. PUL ranked consistently highly and at 24 mo resulted in a significantly higher score compared to mTURP. When using non-mTURP comparators, PUL also yielded significantly higher scores compared to LSP, OP, PAE, and bTURP at 12 mo, and to Aquablation, HoLEP, PVP, LSP, and OP at 24 mo. PUL data were unavailable beyond 24 mo. Furthermore, PUL was not studied in trials with mean prostate volume >60 ml, and therefore the effect of PUL in larger prostates could not be assessed. Apart from OP, which resulted in a significantly lower score at 12 mo compared to HoLEP, all other comparisons did not reach statistical significance at any time point. In meta-regression, there was no significant association between mean baseline questionnaire score and MD in any analysis. In further analyses, mean prostate volume and mean age were also nonsignificant covariates. Heterogeneity was greatest at 1 mo and 60 mo, which may be explained by interstudy differences in age at 1 mo and in baseline IIEF-5 score at 60 mo.

Analyses concerning the full IIEF, MSHQ-EjD, and MSHQ-Bother instruments were hampered by a paucity of data and therefore a robust interpretation of these results is difficult. None of the studies included used the BSFI questionnaire.

3.9.2. Interventions

The incidence of erectile dysfunction after mTURP ranges from 3.4% to 32% in the literature [66]. Owing to the use of normal saline over nonconducting liquids plus the use of bipolar energy, lower morbidity would be expected with bTURP [32]. However, this was not demonstrated statistically.

PVP was a popular intervention, with direct comparison to mTURP in six RCTs [21–23,38,40,41,50,51]. PVP was used at settings of 80 W, 120 W, and 180 W (Table 2), although no subgroup analysis for this parameter variation was performed. Whether newer technology, such as the 180 W XPS GreenLight system, differentially affects sexual function remains to be confirmed in longer-term follow-up [21–23,34].

Enucleation was performed with bipolar energy, as well as holmium, thulium, and diode lasers. These vary in their penetration depth, with deeper penetration yielding better haemostasis but with a greater risk of collateral damage [67]. There were no statistically significant results from comparisons among enucleation techniques or in comparison to mTURP.

OP is most commonly used with large prostates. As expected with an open operation, OP results in greater length of stay, blood loss, and morbidity [19,30,49,52]. LSP is a minimally invasive, although less-studied, alternative. There was no significant difference in comparisons between LSP and OP or in comparison to mTURP, including subgroup analyses for prostate volume. This probably reflects insufficient data, particularly for LSP [62]. Non-endoscopic techniques may pose a greater risk to neurovascular structures, so further study is needed.

The new tissue-sparing UroLift system uses implants to compress lobes and achieve urethral patency. Whether this explains the better performance of PUL is unclear. Considering the limited number of PUL studies and therefore direct evidence, further trials are required before robust recommendations can be made. PUL was also not used with larger prostates.

PAE is a novel radiological procedure that aims to block the prostatic arterial supply, resulting in prostate infarction and atrophy. PAE performed inconsistently, ranking second at 3 mo and last at 12 mo. Furthermore, in subsequent meta-regression analyses for intervention groups and age, PAE demonstrated a significant benefit at 3 mo. A previous meta-analysis of nine observational studies demonstrated significant improvements in IIEF-5 score at 6 and 12 mo compared to baseline [68]. It is therefore crucial that future RCTs focus on sexual function to investigate the impact of PAE.

In Aquablation, the novel AquaBeam system uses transrectal ultrasound and high-pressure water jets to ablate prostatic tissue [35]. This precision and avoidance of thermal energy putatively minimises complications. As the only direct evidence here is derived from a single trial [35–37], addition of further RCT evidence and longer-term follow-up are needed to better characterise its impact.

3.9.3. Previous network meta-analyses

This is the first robust network meta-analysis considering sexual function following a wide range of BPO interventions. Li et al [69] published a network meta-analysis in 2016 evaluating RCT data for IIEF-5 scores. However, newer interventions such as PUL were not considered, and three of the 18 studies were retrospective. Preoperative to postoperative changes in score were also used, which is an outcome hindered by regression to the mean. We also note a recent network meta-analysis by Tanneru et al [70] comparing MSHQ-EjD and MSHQ-Bother data following mTURP, Aquablation, Rezūm, and PUL in four RCTs, all of which are included in our review.

In 2019, Huang et al [71] published a network meta-analysis focussing on maximal flow rate (Qmax) and International Prostate Symptoms Score (IPSS) to 36 mo, as well as perioperative parameters and complications. Eight endoscopic techniques were studied, excluding newer treatments such as PUL. Overall, enucleation techniques led to better Qmax and IPSS than vaporisation and resection methods. All interventions also yielded better haemostasis, shorter catheterisation time, and a lower postoperative haemoglobin decline compared to mTURP. Although these outcomes were outside the scope of our study, this recent paper complements our work well.

3.9.4. Strengths and limitations

We evaluated 16 interventions using high-quality RCT data for four questionnaires, with analyses to 60 mo postoperatively. Meta-regression was used and detailed subgroup and sensitivity analyses were performed. Our results provide a pragmatic study of multiple contemporary interventions, which can aid in treatment decisions.

Network meta-analysis is well established and has informed guidelines from institutions such as NICE and the World Health Organization [13,72,73]. This technique permits robust comparison between interventions lacking direct RCT comparison, minimising judgments based on weaker evidence. Network meta-analysis also improves power and promotes more concise interpretation by facilitating a simultaneous, up-to-date comparison of interventions in a single model. Despite using RCT data, however, the major limitation of network meta-analysis is that results are observational and, ultimately, are not a substitute for well-conducted RCTs.

The main limitations of our study reflect a lack of data. The aforementioned study by Huang et al [71] included 109 trials. Sexual function measures are less widely studied, and interventions such as Aquablation were represented by just one trial. Questionnaires other than the IIEF-5 instrument were also infrequently studied. As the IIEF-5 only reflects erectile function, we cannot provide robust comments on aspects such as ejaculation and orgasm functions.

Insufficient data also affected other analyses; for example, Rezūm was only examined in underpowered MSHQ-EjD and MSHQ-Bother analyses at one time point. Furthermore, we included two RCTs reporting full IIEF outcomes following holmium laser ablation and bipolar transurethral vaporisation. However, incomplete networks for these time points precluded network meta-analysis. Moreover, we did not identify eligible RCTs studying interventions such as robotic simple prostatectomy, intraprostatic injection, and transurethral needle ablation.

We chose uninformative prior distributions to provide an objective, data-driven analysis given a lack of understanding regarding postoperative sexual dysfunction, as recommended by NICE [13]. However, the use of uninformative

prior distributions is limited by the implication that all men are equally likely to experience any degree of sexual function improvement or exacerbation. Nonetheless, our study can aid in appropriate selection of prior distributions in future network meta-analyses.

A random-effects model was chosen to reflect anticipated intertrial heterogeneity. This model choice describes what the average intervention effect is rather than the best estimate of a single intervention effect. The random-effects model here therefore does not reflect the actual intervention effect in any study population. A second limitation of random-effects models is that the weighting of small studies increases. In comparison, fixed-effects analyses produced some further significant results (Supplementary Fig. 1H). However, the model fit was not significantly different between fixed- and random-effects models.

Finally, covariate data used in the meta-regression were at the study level and are therefore subject to confounding and ecological bias. The optimal approach would involve using data for individual patients, but these are rarely presented.

3.9.5. *Future research*

Despite detrimental effects on quality of life, many trials on BPO treatments omit research on erectile function, so this needs further study in RCTs, particularly for newer interventions. For more global assessment of postoperative sexual function, research using additional questionnaires is also needed for domains such as orgasm and ejaculation functions. More data on how PUL performs in larger prostates, as well as its performance over longer-term follow-up, will be important. Finally, our study would benefit from further direct RCT evidence of PUL versus other interventions, especially those that yield superior Qmax and IPSS outcomes [71]. For example, an RCT comparing PUL to bEP or HoLEP would be useful.

4. Conclusions

Our review of postoperative erectile function revealed that the tissue-sparing PUL intervention ranked highly at time points up to 24 mo, at which point benefit over mTURP was observed. In 60-mo follow-up, we did not observe any significant differences in erectile function following interventions when compared to mTURP. Our network meta-analyses provide observational evidence and, owing to heterogeneity, conclusions were weakest at 1 mo and 60 mo. This research would benefit from further RCTs and further collection of long-term data from existing trials, particularly regarding newer interventions such as PUL. Moreover, data on the effect of PUL in larger prostates and further investigations of other sexual function domains are required. Our study details postoperative erectile function outcomes over time, which is important in the counselling of patients regarding BPO surgical options.

Author contributions: Prokar Dasgupta 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: Light, Dasgupta, Elhage.
Acquisition of data: Light, Jabarkhyl, Gilling.
Analysis and interpretation of data: Light.
Drafting of the manuscript: Light.
Critical revision of the manuscript for important intellectual content: Jabarkhyl, Gilling, George, Van Hemelrijck, Challacombe, Malde, Popert, Dasgupta, Elhage.
Statistical analysis: Light, George, Van Hemelrijck.
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Supervision: Gilling, Van Hemelrijck, Challacombe, Malde, Popert, Dasgupta, Elhage.
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Appendix A. Supplementary data

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Platinum Priority – Editorial

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Is Sexual Function Impacted After Minimally Invasive Surgery for Benign Prostatic Obstruction?

Ruben Blachman-Braun, Jesse Ory, Hemendra N. Shah, Ranjith Ramasamy *

Department of Urology, Miller School of Medicine, University of Miami, Miami, FL, USA

In this issue of *European Urology*, Light et al [1] report on the effect of benign prostatic obstruction (BPO) surgical techniques on erectile function through a well-designed systematic review and network meta-analysis. They extracted data from 48 articles that included 5159 patients and 16 surgical techniques. The authors found that prostatic urethral lift (PUL) was associated with a higher International Index of Erectile Function (IIEF) score when compared to monopolar transurethral resection of the prostate (mTURP) at 24 mo (mean difference 3.6 points, 95% credible interval 0.14–7.1) but not at any other time point (1, 3, 6, and 12 mo). All other modalities did not show any differences in erectile function when compared to mTURP.

Lower urinary tract symptoms (LUTS) secondary to BPO are a major health burden, with a prevalence of 44% among men aged 40–59 yr and 70% among men older than 80 yr [2]. As the global population ages and the prevalence of LUTS increases, an understanding of the sexual side effects of the different surgical treatment options for BPO is increasingly relevant. TURP remains the surgical procedure most frequently performed to treat BPO/LUTS [3]. During the past decade we have witnessed a surge of new procedures, such as prostatic artery embolization, holmium laser enucleation of the prostate (HoLEP), GreenLight laser vaporization, Aquablation, PUL, Rezūm, and others. Some minimally invasive therapies have fallen out of favor (transurethral needle ablation [TUNA] and urethral stents) as more evidence of their lower efficacy accumulated [4]. These modalities benefited from nearly a decade of guideline endorsement, but after it became clear that they resulted in minimal to no reduction in prostate size with an inadvertent high retreatment rate, the American Urological Association guidelines ceased to recommend them as treatment options. Whether or not this newer generation of minimally invasive therapies will meet the same fate as TUNA remains to be seen and will depend, in part, on long-term efficacy and sexual function data. In clinical practice, when approaching treatment options using a shared-decision making process, the decision must weigh multiple factors, including prostate size, durability of treatment, the health of the patient, use of anticoagulation, urologist experience, available technology, insurance coverage, ability for inpatient or outpatient treatment, and the potential side-effect profile of each surgical approach [5].

Sexual side effects of BPO surgery are multifaceted; the incidence of retrograde ejaculation ranges widely between treatment modalities and can often be a reason for patients to select one modality over another [6]. However, postoperative erectile dysfunction (ED) remains relatively infrequent. In prostate-cavitating surgeries such as mTURP, sexual dysfunction can occur when the neurovascular bundles are accidentally injured, possibly due to indirect thermal injury during the procedure [6,7]. Furthermore, retrograde ejaculation occurs during mTURP when the bladder neck is opened, which could negatively impact IIEF scores if it leads to a decrease in sexual satisfaction [6,8]. Since the findings reported by Light et al [1] are only based on IIEF scores, it is possible that either a deterioration in erectile function or retrograde ejaculation with mTURP affected these scores and thus may account for the findings favoring PUL.

Light and colleagues [1] clearly warn against overinterpretation, and indeed a modicum of caution is warranted in interpreting the results. The cautious reader will observe that of the 48 articles included in this network meta-analysis, there are only two trials involving PUL: one

* Corresponding author. Department of Urology, Miller School of Medicine, University of Miami, 1120 NW 14th Street, Miami, FL 33136, USA.
Tel. +1 305 2436090; Fax: +1 305 2434653.
E-mail address: ramasamy@miami.edu (R. Ramasamy).

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compared to sham (LIFT), and one compared to mTURP (BPH6). The LIFT study showed that PUL preserved sexual function in men with mild or moderate ED, and led to a modest improvement in men with severe ED. This finding lacks a clear scientific explanation but may be attributable to the fact that patients enrolled in the study were required to stop α blockers for 2 wk and 5α reductase inhibitors for 3 mo before enrolment. The potential sexual side effects of these medications might reverse slowly over time, causing delayed improvement in ejaculation. Moreover, men were allowed to continue taking phosphodiesterase-5 inhibitors during the trial. While PUL preserves sexual function, retreatment rates in both trials were 13.6% at 2 and 5 yr. In addition, Figure 2 [1] reveals that of all the modalities and time points tested, PUL only reached statistical significance at 24 mo after the procedure, with no significant difference at 1, 3, 6, or 12 mo. While a statistical aberration cannot be ruled out, a biological rationale for such late improvement is unlikely. This will only be fully understood after additional trials comparing PUL to other modalities are performed. Other aspects to caution against overinterpretation include the lack of uniformity of prostate sizes in the cohorts and the lack of granular IIEF data among the comparative arms. We do not know if the change in erectile function is merely due to a change in sexual satisfaction, possibly because of the high percentage of retrograde ejaculation in the TURP arm, as erections specifically were not measured. Of great utility to clinicians is the other main finding in this paper that (aside from PUL), all surgical modalities had equivalent erectile function outcomes at all time points on network meta-analysis. This knowledge is critical for the concerned patient interested in surgical treatment for BPO.

With the increase in minimally invasive and in-office–based procedures, special efforts should be made to better understand the long-term sexual effects associated with treatment, as we expect that the use of these procedures will increase in the foreseeable future [9]. This article adds to a growing list of publications suggesting the need for appropriately powered prospective head-to-head randomized clinical trials comparing different BPO surgical modalities, with sexual outcomes prioritized.

We have come a long way since the first BPO procedure was performed [10]. Management of BPO/LUTS is challenging, and every patient should have a personally tailored approach based on clinical characteristics, patient expectations, and potential side effects. Sexual consequences must be discussed before deciding to undergo any procedure, with retrograde ejaculation and erectile function highlighted. Light and colleagues [1] should be congratulated for helping to better elucidate the effect of BPO/LUTS surgery on erectile function, providing additional data that urologists can use while counseling patients before treatment.

Conflicts of interest: The authors have nothing to disclose.

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European Association of Urology

Review – Reconstructive Urology

European Association of Urology Guidelines on Urethral Stricture Disease (Part 1): Management of Male Urethral Stricture Disease

Nicolaas Lumen [a,*], *Felix Campos-Juanatey* [b], *Tamsin Greenwell* [c], *Francisco E. Martins* [d], *Nadir I. Osman* [e], *Silke Riechardt* [f], *Marjan Waterloos* [a,k], *Rachel Barratt* [c], *Garson Chan* [g], *Francesco Esperto* [h], *Achilles Ploumidis* [i], *Wesley Verla* [a], *Konstantinos Dimitropoulos* [j]

[a] *Division of Urology, Gent University Hospital, Gent, Belgium;* [b] *Urology Department, Marques de Valdecilla University Hospital, Santander, Spain;* [c] *Department of Urology, University College London Hospital, London, UK;* [d] *Department of Urology, Santa Maria University Hospital, University of Lisbon, Lisbon, Portugal;* [e] *Department of Urology, Sheffield Teaching Hospitals, Sheffield, UK;* [f] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [g] *Division of Urology, University of Saskatchewan, Saskatoon, Canada;* [h] *Department of Urology, Campus Biomedico University of Rome, Rome, Italy;* [i] *Department of Urology, Athens Medical Centre, Athens, Greece;* [j] *Aberdeen Royal Infirmary, Aberdeen, UK;* [k] *Division of Urology, AZ Maria Middelares, Gent, Belgium*

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Abstract

Objective: To present a summary of the 2021 version of the European Association of Urology (EAU) guidelines on management of male urethral stricture disease.
Evidence acquisition: The panel performed a literature review on these topics covering a time frame between 2008 and 2018, and used predefined inclusion and exclusion criteria for the literature to be selected. Key papers beyond this time period could be included as per panel consensus. A strength rating for each recommendation was added based on a review of the available literature and after panel discussion.
Evidence synthesis: Management of male urethral strictures has extensively been described in literature. Nevertheless, few well-designed studies providing high level of evidence are available. In well-resourced countries, iatrogenic injury to the urethra is one of the most common causes of strictures. Asymptomatic strictures do not always need active treatment. Endoluminal treatments can be used for short, nonobliterative strictures at the bulbar and posterior urethra as first-line treatment. Repetitive endoluminal treatments are not curative. Urethroplasty encompasses a multitude of techniques, and adaptation of the technique to the local conditions of the stricture is crucial to obtain durable patency rates.
Conclusions: Management of male urethral strictures is complex, and a multitude of techniques are available. Selection of the appropriate technique is crucial, and these guidelines provide relevant recommendations.
Patient summary: Injury to the urethra by medical interventions is one of the most common reasons of male urethral stricture disease in well-resourced countries. Although different techniques are available to manage urethral strictures, not every technique is appropriate for every type of stricture. These guidelines, developed based on an extensive literature review, aim to guide physicians in the selection of the appropriate technique(s) to treat a specific type of urethral stricture.

* Corresponding author. Department of Urology, Ghent University Hospital, C. Heymanslaan 10, 9000 Gent, Belgium. Tel. +32 9 3322278, Fax: +32 9 3323889.
E-mail address: Nicolaas.lumen@uzgent.be (N. Lumen).

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1. Aetiology and guidelines on prevention

The following conditions have been identified as etiological factors of urethral stricture disease (USD) and some of these strictures can be prevented (Table 1):

1 *Urethritis due to sexually transmitted infection* was previously a major cause of USD in well-resourced countries accounting for 40% of all cases [1]. The wide-scale promotion of safe sexual practices and timely treatment with antimicrobials is thought to have led to the considerable reduction in the problem [1]. Infective urethritis now accounts for up to 3.7% of cases in well-resourced countries [1] but continues to be the major cause (41.6%) of USD in low-resourced countries [2].
2 *Inflammation due to lichen sclerosus* (LS) is the cause of USD in up to 13.4% of cases and is the most common cause of pan-USD (48.6%) [3].
3 *External trauma to the urethra* is the second most common cause of USD in adults [1]. The bulbar urethra is the site most frequently affected by blunt trauma [4], usually as a result of straddle injuries or kicks to the perineum. Penile fracture is associated with a urethral injury in 15% of cases [5]. Motor vehicle accidents associated with pelvic fractures are the main cause of blunt injuries to the posterior urethra [6].
4 *Iatrogenic injury to the urethra* is one of the most common causes (32–79%) of USD in well-resourced countries [1,7]. Prevention of iatrogenic urethral injury represents the main way in which healthcare providers can prevent USD. Iatrogenic urethral injury most commonly results from urethral instrumentation (eg, catheterisation and cystoscopy), surgery for benign prostatic obstruction (BPO)/prostate cancer, or radiotherapy.
   (a) *Urethral catheterisation*: This accounts for 11.2–16.3% of USD [1,3]. Hollingsworth et al [8] reported a 3.4% urethral stricture rate or erosion after short-term catheterisation (<3 wk). The rate of traumatic insertion of a urethral catheter was found to be 3.2 per 1000 inpatients [9]. Catheter-related trauma can be prevented through several measures. Studies have indicated that around 25% of all indwelling catheterisations in hospitals were unnecessary or inappropriate [10]. A targeted training program on urethral catheterisation was shown to be effective in reducing iatrogenic urethral injuries [9]. Catheter diameter is suggested to be a possible contributing factor to USD due to a pressure effect on the urethral wall. Decreasing the catheter size from 22 Fr to 18 Fr significantly decreased the risk of fossa navicularis strictures (6.9% vs 0.9%, $p = 0.02$) [11]. Catheter material may also have an influence on the occurrence of stricture, as noncoated latex catheters were associated with a greater incidence of urethritis and more stricture formation than silicone catheters [12].
   (b) *Transurethral prostate surgery*: USD following transurethral prostate surgery occurs in 4.5–13% of cases [13], whereas bladder neck stenosis (BNS) occurs in between 0.3% and 9.7% [14]. Transurethral surgery is the most common cause of iatrogenic USD accounting for 41% of all causes [7]. A systematic review showed no significant differences in USD and BNS rates by energy modality (monopolar, bipolar, holmium laser enucleation, and photoselective vaporisation) [13]. Routine preliminary urethrotomy prior to transurethral resection of the prostate (TURP) was not able to lower the stricture rate significantly compared with TURP alone (14% vs 21%) [15].
   (c) *Radical prostatectomy*: Radical prostatectomy (RP) has been associated with vesicourethral anastomosis (VUA) stricture (VUAS) in 1–3% of cases [16].
   (d) *Prostate radiation and ablative treatments*: USD occurs in 1.5% of patients undergoing external beam radiation therapy (EBRT), 1.9% having brachytherapy (BT), and 4.9% who receive combination EBRT-BT at around 4 yr of follow-up [17]. These strictures typically occur in the bulbomembranous urethra [1]. As opposed to RP, stricture incidence after irradiation increases with time [17,18]. For the ablative treatments, the stricture incidence after cryotherapy is 1.1–3.3% and that after high-intensity focused ultrasound is 1–31% [18].
5 *Failed hypospadias repair* (FHR), which although sometimes considered as iatrogenic strictures, represent a very specific subtype and should be considered as a separate entity.
6 *Congenital USD* can only be diagnosed in the absence of other possible aetiologies [19]. Congenital strictures are thought to be consequent to incomplete or incorrect fusion of the urethra formed from the urogenital sinus, with the urethra formed following closure of the urethral folds. They typically have a deep bulbar location and are short.
7 *Idiopathic USD* is seen in, respectively, 34% and 63% of penile and bulbar strictures [20].

Table 1 – Guidelines for prevention of urethral stricture disease

Recommendations	Strength rating
Advise safe sexual practices, recognise symptoms of sexually transmitted infections, and provide access to prompt investigation and treatment for men with urethritis.	Strong
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage only is the purpose.	Weak
Avoid using noncoated latex catheters.	Strong
Do not perform urethrotomy routinely when there is no pre-existent urethral stricture.	Strong

2. Conservative management

2.1. Observation

Purohit et al [21] observed patients with incidentally encountered strictures (≥16 Fr; Table 2). No patient

Table 2 – Guidelines on conservative management

Recommendations	Strength rating
Do not intervene in patients with asymptomatic incidental (>16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

developed symptoms and none of them needed surgical intervention.

Another study observed an important discrepancy between cystoscopic recurrence and need for further intervention [22]. Patients with a large-calibre (>16 Fr) recurrence had 1- and 2-yr need for intervention rates of 4% and 12%, respectively. Of note, patients with small-calibre (≤16 Fr) recurrence had 1- and 2-yr need for intervention rates of only 41% and 49%, respectively. Patients who needed intervention had poorer patient-reported outcome measures suggesting clinical symptoms and bother.

2.2. *Suprapubic catheter*

Fuchs et al [23] evaluated 75 patients who were initially treated by suprapubic diversion for radiation-induced isolated bulbomembranous strictures (BMSs) [23]. Only 51% eventually decided to undergo urethroplasty after a mean follow-up period of 25 mo. Patients with concomitant stress urinary incontinence (SUI) opted more often to keep their suprapubic catheter as the SUI improved in 61% of cases. A suprapubic catheter is also an option in frail patients not able to undergo surgery or in patients who do not want (further) urethral surgery and are willing to accept the complications of a suprapubic catheter.

3. Endoluminal treatment of anterior urethral strictures

This treatment category encompasses direct vision internal urethrotomy (DVIU) and dilatation (Table 3). Steenkamp et al [24] randomised 210 patients with seemingly comparable nonobliterative strictures at all locations of the urethra to either filiform dilatation or DVIU, and showed that DVIU and dilatation are equally effective. As such, the indications for DVIU and dilatation at the anterior urethra are the same.

Patency rates vary considerably between 8% and 77% after DVIU (Supplementary Table 1) and between 35.5% and 92.3% after dilatation at various lengths of follow-up (Supplementary Table 2). Especially at the bulbar urethra, visually controlled dilatation might reduce complications (especially false passage, spongiosal perforation, and urethral bleeding) of blind dilatation [25]. Indication to perform DVIU/dilatation is dependent on various stricture characteristics that are prognostic for a successful outcome. Increasing stricture length, increasing stricture tightness, more than one stricture, location outside the bulbar urethra, and prior failed endoluminal treatment were identified as predictors of stricture recurrence after DVIU/dilatation (Supplementary Table 1). DVIU at the penile urethra appears to have a higher risk for subsequent erectile dysfunction (ED) [26]. Based on these predictors, the most suitable indication for DVIU/dilatation appears to be previously untreated patients with a single, short (maximum 2 cm) bulbar stricture. For these selected patients, a 5-yr patency rate of 71% has been reported [27]. When DVIU was used for a short stricture recurrence after urethroplasty, patency rates of around 50% were reported [28].

A systematic review reported no significant difference in patency rates after a first DVIU using laser versus cold knife (58.6% vs 42.7%; $p = 0.09$). At the bulbar urethra, laser and cold knife DVIU yielded patency rates of 52.9% and 60%, respectively ($p = 0.66$) [29].

Several strategies have been developed to improve patency rates after DVIU/dilatation. These strategies include intralesional injection with steroids [30]/mitomycin C (MMC) [31], intermittent self-dilatations (±intraurethral corticosteroids [30]) [32], and temporary urethral stents [33]. Intermittent self-dilatations and local corticosteriods tend to stabilise the stricture and prolong the time to recurrence rather than keeping the patient stricture free. Intralesional MMC has encouraging results, but its use in the urethra is still off-label [31]. Stents must be used with caution because a history of failed stenting is a predictor of increased stricture complexity and need for more complex urethroplasty [34].

Table 3 – Guidelines on endoluminal treatment of anterior urethral strictures

Recommendations	Strength rating
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (>2 cm) segment strictures.	Strong
Perform DVIU/dilatation for a primary, single, short (<2 cm), and nonobliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty.	Weak
Use either “hot” or “cold” knife techniques to perform DVIU depending on the experience and resources.	Weak
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (>2) DVIU/dilatations if urethroplasty is a viable option.	Strong
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/DVIU if urethroplasty is not a viable option.	Weak
Use intraurethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak
Do not use intralesional injections outside the confines of a clinical trial.	Weak
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after DVIU to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

4. Urethroplasty for anterior urethral strictures

4.1. Distal urethral strictures (meatal stenosis and fossa navicularis strictures)

For meatal stenosis, the Malone meatoplasty (dorsal + ventral meatotomy) provides patency rates up to 100%, and 83% of patients were pleased with the cosmetic result (Table 4) [35].

Skin flap meatoplasty showed patency rates ranging from 85% to 100% [36,37]. Patient satisfaction with postoperative outcomes and cosmesis was high (84–100%), there were no cases of ED, and functional complaints were minimal (mainly spraying of the urine flow) [36,37].

Patency rates with the use of grafts ranged from 69% to 91% [37,38], and all patients were satisfied with cosmesis [38].

4.2. Penile strictures

Anastomotic urethroplasty has been discouraged due to the risk of chordee postoperatively. Nevertheless, it has been anecdotally performed in selected patients with very short (<1 cm) strictures reporting a 93% patency rate [39]. In general, the choice is between single-stage and staged augmentation urethroplasty (Table 4).

4.2.1. Staged augmentation urethroplasty

In general, reconstructive urologists tend to follow this approach in men with more complex USD (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, and poor quality of the urethral plate) [40]. An interval of at least 4–6 mo has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed well [40,41]. A systematic review has shown an average patency rate of 90.5% with the use of all types of grafts after 22 mo of follow-up [41]. Up to 20% of patients will need a revision after the first stage [42]. In addition, after the first stage, a substantial number of patients (up to 45%) will refuse to proceed with further reconstructive surgery because they were satisfied with their functional status after the first stage [43].

Table 4 – Guidelines on urethroplasty for meatal stenosis, fossa navicularis, and penile strictures

Recommendations	Strength rating
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or a staged approach, taking into consideration previous interventions and stricture characteristics.	Strong
Proceed to the second stage of the procedure after an interval of at least 4–6 mo and provided that outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures >1 cm due to the risk of penile chordee postoperatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in case of adverse intraoperative findings.	Strong
Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with lichen sclerosus–related strictures.	Weak

4.2.2. Single-stage augmentation urethroplasty

Single-stage urethroplasty avoids the need for multiple operations, the associated periprocedural risks, and the cosmetic and functional implications that by definition follow the first part of staged urethroplasties [44]. A critical factor is the careful selection of patients as men with long and/or complex strictures might not be good candidates for single-stage reconstruction. Sometimes, this selection can only be done based on intraoperative findings. Therefore, any scheduled single-stage procedure might be converted into a staged one [44]. A systematic review reported an overall patency rate of 75.7%, with an average follow-up of 32.8 mo [41]. No high-level evidence exists to state that one technique is superior to another, but it seems that the dorsal graft location is more commonly used than the ventral one [41]. FHR- and LS-related strictures are often considered complex strictures that should preferably be treated by staged urethroplasty [40]. However, in the absence of adverse local tissue conditions, a single-stage approach yields acceptable patency rates for both FHR- [43] and LS-related strictures [45].

4.3. Bulbar strictures

4.3.1. Short (<2–3 cm) bulbar strictures

In fit patients, the choice is between excision and primary anastomosis (EPA) and free graft urethroplasty (FGU).

Table 5 – Guidelines on urethroplasty for bulbar strictures

Recommendations	Strength rating
Use transecting excision and primary anastomosis (tEPA) for short post-traumatic bulbar strictures with (nearly) complete obliteration of the lumen and full-thickness spongiofibrosis.	Strong
Use nontransecting excision and primary anastomosis or free graft urethroplasty (FGU) instead of tEPA for short bulbar strictures not related to straddle injury.	Weak
Use FGU for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA, but with a short, nearly obliterative segment within the whole strictured segment.	Weak
Use the dorsal, dorsal-lateral, or ventral approach according to surgical practice, expertise, and intraoperative findings.	Strong
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single-stage urethroplasty and those who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single-stage urethroplasty is possible.	Weak
Consider staged procedure in patients unsure about perineal urethrostomy versus urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

4.3.1.1. Excision and primary anastomosis. Transecting EPA (tEPA) includes full-thickness resection of the segment of the bulbar urethra where the stricture and surrounding spongiofibrosis are located (Table 5). A review reported a composite patency rate of 93.8% [46]. ED (usually transient), cold feeling in the glans (3.2%), and decreased glandular tumescence (17%) are complications associated with tEPA [47].

Bulbar strictures, with the exception of post-traumatic bulbar strictures, are usually not associated with complete obliteration and full-thickness spongiofibrosis. Therefore, complete excision of the surrounding spongious tissue with disruption of the antegrade blood flow of the urethra and corpus spongiosum can be regarded as excessive surgical trauma, and in this perspective, nontransecting EPA (ntEPA) has been described. Two series comparing tEPA with ntEPA reported comparable patency rates of 88.4–93.8% and 93.2–97.9%, respectively, albeit follow-up was shorter with ntEPA [48,49]. After 6 mo, ntEPA had significantly lower ED rates than tEPA (4.3% vs 14.3%) [48].

4.3.1.2. Free graft urethroplasty. Despite the very high patency rates of EPA, FGU has been performed for short bulbar strictures as well. This is mainly driven by reports of ED after EPA. A meta-analysis of ten papers comparing tEPA with FGU for short strictures found that tEPA is better than FGU in terms of patency rates (91.5% vs 70%), whilst FGU has fewer erectile complications (9% vs 25%) [50]. To date, no trials comparing ntEPA with FGU regarding patency outcomes and complications have been published.

4.3.2. Long bulbar strictures

For strictures not amenable to EPA, FGU is the technique of choice. The patency rate of FGU of the bulbar urethra is 88% with 40 mo of follow-up [41].

Augmented anastomotic repair (AAR) is also an option for these strictures. AAR can be offered if the stricture is too long (circa 2–4 cm) for tension-free EPA or for longer strictures with a short (nearly) obliterative segment. A patency rate after AAR of 91.9% with 28 mo of follow-up has been reported [51]. An alternative for strictures with a nearly obliterative or high-grade segment is double ventral-dorsal onlay, and this technique yielded a patency rate of 91% after 22 mo of follow-up [41].

Regarding the optimal site of graft placement (dorsal onlay, dorsal inlay, ventral onlay, and dorsolateral onlay), a systematic review was conducted. No significant differences were found regarding patency rate, ED, postvoid dribbling, or other complications [52].

4.3.3. Staged urethroplasty for bulbar strictures

Staged urethroplasty may be considered in case of local adverse conditions (fistula, false passage, abscess, cancer, severe spongiofibrosis, previous radiotherapy, and FHR; Supplementary Table 3). Patency rates of 33.3–90.1% at a mean follow-up of 11.2–32 mo have been described (Supplementary Table 3).

There is some controversy whether LS-related strictures should always be treated with staged urethroplasty. Warner et al [53] reported, for LS-related bulbar strictures, a 52.2% patency rate for staged urethroplasty, whereas this was 86% for single-stage buccal mucosa urethroplasty ($p < 0.01$).

Kozinn et al [54] reported that 19% of patients declined retubularisation because they were satisfied with their voiding outcomes after first stage. In addition, 19% of men required a revision of their first-stage urethroplasty [54].

4.4. Penobulbar or panurethral strictures

The options for surgical reconstruction are various and often include combinations of different techniques or grafts (Table 6) other than oral mucosa graft (OMG) [53]. The patency rates are usually lower than in shorter reconstructions (Supplementary Table 4). Another option in patients refusing or unfit for complex reconstructive surgery is perineal urethrostomy (PU).

4.5. Perineal urethrostomy

PU (Table 7) offers a solution in men with complex USD in whom:

1 There are no further options to restore urethral patency due to either multiple previous failed urethroplasties [55] or there are multiple comorbidities precluding a more expansive surgical undertaking after failed endoscopic management [56]
2 There is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty [55]

Table 6 – Guidelines on urethroplasty for penobulbar/panurethral strictures

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

Table 7 – Guidelines on perineal urethrostomy

Recommendations	Strength rating
Offer perineal urethrostomy as a management option to men with complex anterior urethral stricture disease.	Strong
Offer perineal urethrostomy to men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose the type of perineal urethrostomy based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet Blandy perineal urethrostomy or “7-flap” perineal urethrostomy in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider “7-flap” urethroplasty in obese men.	Weak

Different techniques have been described (Johanson PU, Gil-Vernet-Blandy PU, loop PU, and 7-flap PU). Patency rates of 70–95% after 20–63 mo of follow-up have been described (Supplementary Table 5). Barbagli et al [55] reported that 97.1% of men were satisfied or very satisfied with the outcome of their PU. Little data are available to determine the best technique for PU. The 7-flap PU has been developed for use in very obese patients or men with stricture extension into the proximal bulbar or membranous urethra [57]. Another option for strictures extending into the proximal bulbar or membranous urethra is the OMG-augmented Gil-Vernet-Blandy PU [56].

5. Endoluminal management of posterior urethral stenosis

Dilatation can be used for VUAS or radiation-induced BMS (Table 8). Patency rates vary widely between 0% and 89% (Supplementary Table 6). The risk of de novo urinary incontinence was low (0–11%), and no other complications were reported. It is of note that most series report on visually controlled dilatation in VUAS without complete obliteration (Supplementary Table 6) [58–62].

DVIU for nontraumatic posterior stenosis is mainly performed for VUAS and radiation-induced BMS. Patency after a first DVIU ranges between 25% and 80% (Supplementary Table 7). In series where pre-DVIU continence data were available, de novo urinary continence after DVIU ranges between 0% and 10% (Supplementary Table 7). It is noteworthy that 20–52% of pre-DVIU incontinent patients might experience improvement after DVIU [63,64]. For BNS, Redshaw et al [65] reported inferior patency rates for cold knife versus hot knife incision (50% vs 63%; $p = 0.03$).

Table 8 – Guidelines on endoluminal management of posterior urethral stenosis

Recommendations	Strength rating
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as first-line treatment for a nonobliterative vesicourethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous stricture (BMS)	Weak
Do not perform deep incisions at the 6 and 12 o'clock position during DVIU for VUAS or radiation-induced BMS.	Strong
Perform transurethral resection or hot-knife DVIU as first-line treatment for patients with nonobliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repetitive endoluminal treatments in nonobliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of de novo urinary incontinence (UI) or exacerbation of existing UI after endoluminal treatment.	Weak
Do not use stents for strictures at the posterior urethra.	Weak
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, nonobliterative post-traumatic stenosis.	Weak
Do not perform more than two DVIUs and/or dilatations for a short and nonobliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

DVIU using the cut-to-the-light technique for complete obliterative stenosis is not advised because of a very low likelihood of durable patency and the risk of false passage towards the rectum [52]. Aggressive incisions at the 6 and 12 o'clock positions should be avoided because of the risk of, respectively, rectal injury and urosymphyseal fistulation, which is especially a concern after radiotherapy [66].

Transurethral resection (TUR) can be performed in case of VUAS and BNS. Patency rate after TUR for VUAS is 40.2%, but at the cost of an incontinence rate of 13.8–50% [62,67]. Patency and incontinence rates of TUR for BNS are, respectively, 58.3% and 1.7% [67].

Repetitive endoluminal treatments in nonobliterative VUAS, radiation-induced BMS, or BNS have the ability to stabilise the posterior stenosis and are easier to perform than reconstructive surgery, but ultimately 6–10% will be required urinary diversion [68] or chronic suprapubic cystostomy [69]. Further attempts to stabilise the nontraumatic posterior stenosis include intralesional steroid injections (ISDs), intralesional injections, and stents. ISDs are possible but usually associated with reduced quality of life and poor patient compliance [70]. Patency rates with corticosteroid injections range between 50% and 100% [62,71]. Patency rates with MMC vary between 58% and 79% [65,72]. Redshaw et al [65] also reported devastating complications (osteitis pubis, bladder neck necrosis, and rectourethral fistula) in 7% of patients after MMC injection. Patency rate of stents is 47% [73,74] at the cost of a urinary incontinence rate of 19–82% [73,74].

For a nonobliterative, short ($\leq$1.5 cm) post-traumatic stenosis, one attempt of DVIU/dilatation can be performed. A composite patency rate of 20% has been reported (but with a mix of obliterative and nonobliterative stenoses) [6]. De novo urinary incontinence was reported in 4% of cases [6]. Repetitive endoluminal treatments are unlikely to be curative, delay the time to definitive cure, and can lead to more complications [75].

6. Urethroplasty for posterior urethral stenosis

6.1. ReDo VUA for vesicourethral anastomotic stenosis after RP

This may be performed via a retropubic, perineal, combined abdominoperineal, or robot-assisted approach. A repeat (ReDo) VUA in nonirradiated patients yields patency rates of 60–91% (Table 9 and Supplementary Table 8). A ReDo VUA should be done only in patients with adequate bladder function and in the absence of (peri)urethral pathology (urethral necrosis, calcification, and fistulation). With the transperineal approach, urinary incontinence is inevitable, whereas this is only 0–58% with the retropubic approach (Supplementary Table 8).

6.1.1. Posterior stenosis after surgery for BPO

Y-V or T-plasty is used for BNS refractory to endoscopic treatments. Patency rates vary between 83% and 100%, with 14–45 mo of follow-up. De novo incontinence rate ranges from 0% to 14% (Supplementary Table 9).

Table 9 – Guidelines on urethroplasty and reconstructive surgery for posterior urethral stenosis

Recommendations	Strength rating
Perform repeat (ReDo) vesicourethral anastomosis (VUA) in nonirradiated patients and irradiated patients with adequate bladder function with obliterative VUA stricture or VUA stricture refractory to endoluminal treatment.	Weak
Warn patients that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage after at least 3–6 mo.	Strong
Offer ReDo VUA by retropubic approach if the patient is preoperatively continent.	Weak
Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis (BNS).	Weak
Warn patients about de novo UI after reconstruction for BNS or bulbomembranous stricture (BMS) with previous benign prostatic obstruction surgery as aetiology.	Strong
Use either excision and primary anastomosis (EPA) or augmentation urethroplasty for short (<2.5 cm) radiation-induced BMS refractory to endoscopic treatment depending on surgeon's experience.	Weak
Perform augmentation urethroplasty for long (>2.5 cm) radiation-induced BMS.	Weak
Warn patients about the risk of de novo incontinence and new-onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to irradiation or high-energy treatment.	Weak
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak
Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms, and/or haematuria.	Weak
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and EPA for obliterative stenosis.	Strong
Perform progressive perineal EPA for nonobliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdominoperineal reconstruction.	Strong
Reserve abdominoperineal reconstruction for complicated situations including very long distraction defect, paraurethral bladder base fistula, trauma-related rectourethral fistula, and bladder neck injury.	Weak
Perform another urethroplasty after the first failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant rectourethral fistula.	Weak

BMSs are managed as bulbar strictures and can be treated by EPA or augmentation urethroplasty. As reconstruction is in proximity of the external sphincter and the bladder neck was already damaged during BPO surgery, the risk of incontinence (up to 25%) is present [76].

6.2. Radiation/high-energy–induced posterior strictures

Most radiation-induced BMSs are short, and in these cases EPA is possible. Patency rates vary between 67% and 95% [76–79]. De novo urinary incontinence was reported in 33–36% of cases [76–78,80].

EPA will not be possible for BMS with a long bulbar segment. Both dorsal and ventral onlay have been described. Patency rates with augmentation urethroplasty vary between 50% and 83% [77,79,81,82], with de novo incontinence ranging between 11% and 50% [77,81,82].

Prostatic strictures refractory to TUR and with good bladder capacity might be salvaged by RP considering the associated morbidity (rectal injury, VUAS, and incontinence). Mundy and Andrich [83] treated nine patients, with patency in six (67%) and one (11%) needing an artificial urinary sphincter for severe incontinence.

Cases with impaired bladder function, urethral necrosis, and/or periurethral pathology should be considered for supravesical diversion, especially if a suprapubic catheter is not tolerated due to bladder pain or spasms. Intractable haematuria or fistulation might be other reasons to abandon the urethral outlet [83].

6.2.1. Post-traumatic posterior stenosis

Progressive perineal EPA is the standard treatment for an obliterative stenosis and for a nonobliterative stenosis as the first approach or after failure of primary endoluminal treatment. The overall patency rate after deferred EPA is 85.7% [6]. Incontinence is rare (6.8%) with EPA and is usually due to incompetence of the bladder neck, although an incompetent bladder neck does not necessarily result in incontinence after urethroplasty [6]. Erectile function does not deteriorate after EPA or might even improve [84].

A combined transpubic abdominoperineal approach is necessary only in complicated cases such as those with associated paraurethral bladder base fistula, trauma-related rectourethral fistula, and bladder neck injury [85]. Total pubectomy during transpubic abdominoperineal reconstruction has a higher complication rate (bleeding, pelvic instability, and dead space) than partial (superior or inferior) pubectomy, with no gain in surgical exposure [86].

In case of a recurrent stenosis, a ReDo urethroplasty is possible using different types of techniques (Supplementary Table 8). In case of excessive dead space after resection of the fibrosis, gracilis muscle [87] or omental flaps [88] have been advised. The patency rate of different types of ReDo urethroplasty varies between 37.5% and 100% (Supplementary Table 8). An alternative is to abandon the normal urinary outlet and opt for Mitrofanoff vesicostomy, PU (if local perineoscrotal skin is suitable), or permanent suprapubic diversion [89].

7. Tissue transfer

7.1. Comparison of grafts with flaps

Two small randomised controlled trials reported similar patency rates between grafts and flaps (Table 10). However, flaps were associated with more morbidity (superficial penile skin necrosis, penile torsion, penile hypoesthesia, and postvoid dribbling) and longer operation time [90,91].

Table 10 – Guidelines on tissue transfer in urethroplasty

Recommendations	Strength rating
Use a graft above a flap when both options are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal vs lingual vs lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable, or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong
Do not use cell-free tissue-engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty, or in case of stricture length >4 cm.	Weak
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

Castagnetti and Rigamonti [92] showed that grafts used as a tube have a significantly higher complication rate than onlay grafts (odds ratio: 5.86; 95% confidence interval: 1.5–23.4). Iqbal et al [93] have shown an encouraging 87% stricture-free rate in 23 patients who were offered single-stage tubed skin flap urethroplasty. Therefore, if there is a need to reconstruct a complete urethral segment with a tissue-transfer tube in a one-stage operation, flaps are usually the preferred option. As flaps carry their own vascular supply to the reconstruction site, they do not rely on the local vascularisation of the recipient site. Therefore, they need to be considered in case of poor urethral vascularisation (eg, after irradiation or dense scarring after previous urethroplasty) [94].

7.2. Comparison of different types of flaps

Fu et al [95] demonstrated that penile skin flaps had a significantly better urethral patency rate than scrotal and perineal skin flaps (respectively, 87.7%, 69%, and 66.7%). The hair-bearing perineal and scrotal skin flaps are associated with hairball formation and chronic infection, which may cause failure of the repair [96].

7.3. Comparison of different types of grafts

In case of LS, Trivedi et al [97] demonstrated a significantly higher urethral patency rate when using nongenital mucosal grafts for reconstruction (82.6%) than when using genital skin grafts (4%) [97].

A pooled analysis of nonrandomised studies comparing buccal mucosa ($n = 483$) with penile skin ($n = 428$) found a better urethral patency rate for buccal mucosa (85.9% vs 81.8%). However, the results might be biased because of the longer follow-up time and longer stricture length in the penile skin group [98].

OMGs comprise buccal mucosa graft (BMG), lingual mucosa graft (LMG), and lower lip mucosa graft. A systematic review of studies comparing LMG with BMG showed no significant differences in urethral patency and overall long-term complication rate [99]. The use of lower lip mucosa can lead to permanent sequelae (persistent discomfort, neurosensory deficits, salivary flow changes, and important aesthetic changes) at the donor site, which have not been described with lingual mucosa [100].

Beyond the OMG and penile skin graft, a multitude of other autologous grafts have been described with a patency rate of 81–91% (Supplementary Table 9). Owing to the limited experience with these grafts, they should be considered only if oral mucosa and penile skin are not available, indicated, or desired.

The main advantage of cell-free tissue-engineered grafts is the off-the-shelf availability [101]. The results are disappointing in case of an unhealthy urethral bed [102] or a stricture length of >4 cm [103]. A prospective, multicentre study evaluating autologous tissue-engineered OMG reported 12- and 24-mo urethral patency rates of, respectively, 67.3% and 58.2%. Oral adverse events were minimal [104].

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European Association of Urology

Review – Reconstructive Urology

European Association of Urology Guidelines on Urethral Stricture Disease (Part 2): Diagnosis, Perioperative Management, and Follow-up in Males

Felix Campos-Juanatey[a,†,*], *Nadir I. Osman*[b,†], *Tamsin Greenwell*[c], *Francisco E. Martins*[d], *Silke Riechardt*[e], *Marjan Waterloos*[f,k], *Rachel Barratt*[c], *Garson Chan*[g], *Francesco Esperto*[h], *Achilles Ploumidis*[i], *Wesley Verla*[f], *Konstantinos Dimitropoulos*[j], *Nicolaas Lumen*[f]

[a] *Urology Department, Marques de Valdecilla University Hospital, Santander, Spain;* [b] *Department of Urology, Sheffield Teaching Hospitals, Sheffield, UK;* [c] *Department of Urology, University College London Hospital, London, UK;* [d] *Department of Urology, Santa Maria University Hospital, University of Lisbon, Lisbon, Portugal;* [e] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [f] *Division of Urology, Gent University Hospital, Gent, Belgium;* [g] *Division of Urology, University of Saskatchewan, Saskatoon, Canada;* [h] *Department of Urology, Campus Biomedico, University of Rome, Rome, Italy;* [i] *Department of Urology, Athens Medical Centre, Athens, Greece;* [j] *Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;* [k] *Division of Urology, AZ Maria Middelares, Gent, Belgium*

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Abstract

Context: Urethral stricture management guidelines are an important tool for guiding evidence-based clinical practice.
Objective: To present a summary of the 2021 European Association of Urology (EAU) guidelines on diagnosis, classification, perioperative management, and follow-up of male urethral stricture disease.
Evidence acquisition: The panel performed a literature review on the topics covering a time frame between 2008 and 2018, and using predefined inclusion and exclusion criteria for the literature. Key papers beyond this time period could be included if panel consensus was reached. A strength rating for each recommendation was added based on a review of the available literature after panel discussion.
Evidence synthesis: Routine diagnostic evaluation encompasses history, patient-reported outcome measures, examination, uroflowmetry, postvoid residual measurement, endoscopy, and urethrography. Ancillary techniques that provide a three-dimensional assessment and may demonstrate associated abnormalities include sonourethrography and magnetic resonance urethrogram, although these are not utilised routinely. The classification of strictures should include stricture location and calibre. Urethral rest after urethral manipulations is advised prior to offering urethroplasty. An assessment for urinary extravasation after urethroplasty is beneficial before catheter removal. The optimal time of catheterisation after urethrotomy is $<$72 h, but is unclear following urethroplasty and depends on various factors. Patients undergoing urethroplasty should be followed up for at least 1 yr. Objective and subjective outcomes should be assessed after urethral surgeries, including patient satisfaction and sexual function.
Conclusions: Accurate diagnosis and categorisation is important in determining management. Adequate perioperative care and follow-up is essential for achieving successful

† These authors are joint first authors.
* Corresponding author. Urology Department, Marques de Valdecilla University Hospital. Av, Valdecilla ndeg25. CP: 39008. Santander. Cantabria. Spain. Phone: (+34) 942315278
Fax: (+34) 942203478.
E-mail address: fcampos@humv.es (F. Campos-Juanatey).

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outcomes. The EAU guidelines provide relevant evidence-based recommendations to optimise patient work-up and follow-up.
Patient summary: Urethral strictures have to be assessed adequately before planning treatment. Before surgery, urethral rest and infection prevention are advised. After urethral surgery, x-ray dye tests are advised before removing catheters to ensure that healing has occurred. Routine follow-up is required, including patient-reported outcomes. These guidelines aim to guide doctors in the diagnosis, care, and follow-up of patients with urethral stricture.

1. Diagnosis of male urethral strictures

1.1. Patient history

This should assess symptomatology, identify possible aetiology, note prior treatments and complications, and identify associated factors that could influence surgical outcome (Fig. 1 and Table 1).

Male urethral stricture disease (MUSD) presents in a variety of ways. A retrospective series (n = 611) revealed that lower urinary tract symptoms (LUTS) were the main mode of presentation (54.3%). Other less common modes

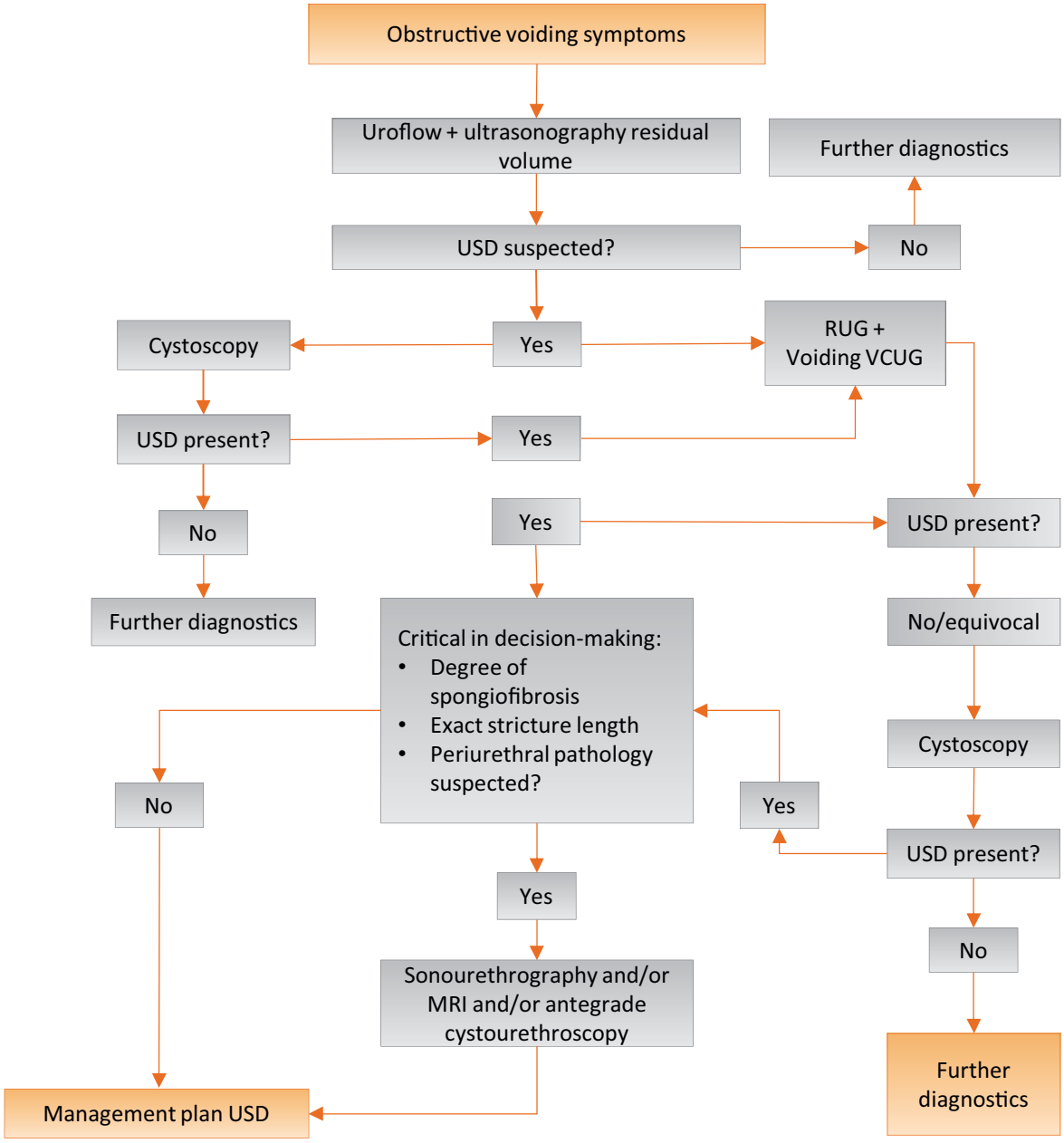

Fig. 1 – Diagnostic flowchart of patients with suspected urethral stricture disease.
MRI = magnetic resonance imaging; RUG = retrograde urethrography; USD = urethral stricture disease; VCUG = voiding cystourethrogram.

Table 1 – EAU Urethral Stricture Guidelines Panel recommendations on diagnosis of male urethral strictures

Recommendations	Strength rating
Use a validated patient-reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong
Perform uroflowmetry and estimation of postvoid residual in patients with suspected urethral stricture disease.	Strong
Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine retrograde urethrography with voiding cystourethrography to assess (nearly) obliterative strictures, stenoses, and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak
Consider MRI urethrography as an ancillary test in posterior urethral stenoses.	Strong

EAU = European Association of Urology; MRI = magnetic resonance imaging.

were urinary retention (22.3%), urinary tract infection (UTI; 6.1%), and difficulty in catheterisation (4.8%) [1]. In another retrospective analysis (n = 214), the most common symptoms were weak stream (49%), incomplete emptying (27%), and urinary frequency (20%) [2]. Postvoid dribble is present in 73% of cases [3].

Pain is also a common feature affecting 22.9–71% of patients [1,4]. Pain can be felt in the bladder and/or urethra and is associated with more significant LUTS. Pain is more likely to be a feature in younger men and usually resolves following reconstructive surgery [4]. Other presentations (9%) include visible haematuria (3.1–5%), urethral abscess/necrotising fasciitis (2.3%), urgency (14%), and incontinence (1–4%) [1,2].

The date of the most recent intervention (ie, dilatation) is important, as this will impact the timing of urethrography or surgery (see section 3.1).

Sexual problems are common in MUSD [5], whilst sexual function may be impacted by reconstructive surgery [6]; therefore, it is important to document sexual function using validated tools.

Health status is important as it influences the choice between a palliative and a curative treatment. Any factor that may impair healing should be identified (ie, diabetes, immunosuppression, and smoking). Oral tobacco usage or chewing of betel leaves can impact the decision regarding whether or not oral mucosa graft can be harvested. It is also important to note previous substitution flap or graft sites/material for future surgical planning.

1.2. Physical examination

The abdomen should be palpated to assess for a full bladder, and the presence of a suprapubic catheter (SPC) should be noted as it may be useful for antegrade cystoscopy or intraoperative sound placement. Genital examination should assess the size of the phallus, presence of chordee, presence of foreskin, any urethrocutaneous fistula, the position and size of the meatus, and any scarring. A biopsy to confirm lichen sclerosus (LS) may be performed if this influences the management approach [7] and is critical if there is any suspicion of malignancy.

The urethra is felt for signs of induration, which is typical with significant fibrosis. Digital rectal examination (DRE) palpating the prostate for signs of enlargement, whether benign or malignant, is essential as this may be the cause of patients' LUTS. In cases of posterior urethral stenosis, DRE can assess rectal adherence to the prostate and tissue mobility [8].

1.3. Further diagnostic evaluation

1.3.1. Patient-reported outcome measures

Jackson et al [9] validated the urethral stricture surgery (USS)-specific patient-reported outcome measures (PROM), and this has been further validated in several other languages.

1.3.2. Urinalysis and urine culture

Urinalysis is an essential component of the evaluation. If infection is identified, urine culture to isolate the causative organism and sensitivity to antibiotics should be requested [10].

1.3.3. Uroflowmetry and postvoid residual estimation

Although the classic pattern is a prolonged plateau shape with reduced maximum urinary flow (Q_{max}), the interpretation of flow patterns is subjective and an unreliable tool to detect MUSD [11]. To overcome this, Lambert and colleagues [11] developed a statistical model based on uroflow and found this to predict urethral stricture with sensitivity of 80–81% and specificity of 77–78%. Uroflowmetry is usually followed by ultrasound measurement of postvoid residual (PVR), which is helpful in identifying patients in chronic urinary retention.

In most patients with MUSD, pressure flow studies are not necessary, except in patients with suspected bladder dysfunction. A common reason to undertake pressure flow studies is when detrusor hypo/acontractility is suspected, as these patients may need to perform intermittent self-catheterisation (ISC) postoperatively. The only urodynamic parameter found to distinguish MUSD from benign prostatic obstruction (BPO) is urethral closure pressure, which is lower in the former due to the constrictive nature of the obstruction (22.07 vs 28.4 cmH_2O, p = 0.0039, r = 0.61, BPO vs stricture) [12].

1.3.4. Urethrography

Retrograde urethrogram (RUG) assesses stricture presence, location, length, and any associated abnormalities (ie, false passages and diverticula).

The sensitivity and specificity of RUG in diagnosing strictures are 91% and 72%, respectively [13]. The positive and negative predictive values were, respectively, 89% and 76% [13]. RUG underestimates stricture length compared with operative findings [14].

The main limitations of RUG are the challenges in assessing very distal strictures and the proximal limit of strictures, which do not allow passage of enough contrast. If RUG is combined with voiding cystourethrography (VCUG), then the urethra proximal to the stricture can be visualised and stricture length in (nearly) obliterative strictures can be assessed more accurately. This technique also allows assessment of the gap in pelvic fracture urethral injury (PFUI) [15]. Other limitations of RUG are that it can provide only a two-dimensional assessment of stricture, and the results may be affected by the amount of penile stretch [16], degree of pelvic rotation, and body habitus [17]. Risks of the procedure include infection, discomfort [12], and contrast reaction from intravasation of contrast, in addition to radiation exposure. Clamp devices (Brodny, Knutson) to facilitate injection of the contrast are available and have been found to be less painful than using a Foley catheter to occlude the urethra whilst performing RUG [18].

1.3.5. Cystourethroscopy

Cystourethroscopy allows for accurate visual detection of a suspected stricture or can rule out a stricture as a cause of obstructive voiding [13]. Narrowing of the urethral lumen can be visualised before the onset of changes in flow rate and symptoms [19]. The presence of LS or other pathology (ie, foreign body or hair) can also be evaluated, but not the stricture length as the calibres of most cystoscopes is greater than most symptomatic strictures [20]. To overcome this, some have used smaller-calibre ureteroscopes (6.5 and 4.5 Fr) [20]. The advantage of this is that it also allows an assessment of the bladder prior to surgery and may identify other pathology such as bladder stones. Cystourethroscopy is particularly important for diagnosing bulbomembranous stricture, which can be missed on RUG.

Combined retrograde urethroscopy and antegrade cystoscopy via an SPC tract is used by some to evaluate PFUI and plan the surgical approach. This allows an evaluation of the length of the defect, bladder neck competence, bladder neck scarring, presence of bony spicules, or other fistulae/false passages or stones [21].

1.3.6. Ultrasound

Sonourethrography (SUG; ultrasound of the urethra) is a noninvasive method of assessing MUSD including stricture location and length, and the degree of associated spongiofibrosis, which provides three-dimensional information [22]. It can be performed in the outpatient setting and is of relatively low cost.

SUG was shown to diagnose stricture presence with greater accuracy [18,23] and is more accurate at estimating stricture length compared with RUG (respectively, 94% and 59% correlation with intraoperative findings; $p < 0.001$) [14]. Intraoperative SUG findings were reported to alter the planned reconstructive approach (based on preoperative RUG) in 19% of men undergoing anterior urethral reconstruction [17].

The main limitations of SUG are lower sensitivity for the detection of bulbar strictures, operator dependency, and the need for urethral distension requiring intraurethral anaesthesia. In addition, SUG needs specialised training, which is likely to be why it is currently not used widely.

1.3.7. Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to image PFUIs, posterior urethral stenoses, and anterior urethral strictures.

MRI urethrogram was found to be as accurate as RUG at detecting stricture site and assessing stricture length in anterior urethral strictures [24]. MRI is more accurate at diagnosing associated pathologies (ie, diverticula, tumours, fistulae, and stones) [25].

In addition, in a study of patients with posterior urethral stenosis, MRI measurement of stenosis length was more accurate than that measured by RUG [26]. In patients with PFUI, MRI measurement of pubourethral stump angle predicted the need for an elaborated approach [27].

MRI provides the greatest anatomical detail of all modalities, but is expensive and more complex to interpret. The technique is not commonly used for routine situations.

2. Classification of male urethral strictures

2.1. According to stricture location

Classification according to stricture location is important as this will affect further management (Table 2) [28].

Strictures extending towards the membranous urethra are termed bulbomembranous strictures.

Penobulbar strictures should be differentiated from multifocal strictures, defined by two or more narrowed segments—either in the same urethral segment or in different segments—but preserving healthy urethral areas between them.

2.2. According to stricture tightness

It has been demonstrated that men usually do not experience subjective obstructive symptoms until the urethral lumen has a diameter below 10 Fr [29].

The European Association of Urology (EAU) stricture panel proposes the following classification upon degree of male urethral narrowing (Table 3).

3. Perioperative management of male urethral strictures

3.1. Urethral rest

After any form of urethral manipulation (urethral catheter, ISC, dilation, and DVIU), a period of urethral rest is necessary

Table 2 – Male urethra stricture locations and anatomic landmarks for classification

Urethral segment		Location—anatomic landmarks
Anterior urethra	Meatal strictures	External urethral meatus; may extend into the fossa navicularis of the glans
	Penile strictures	Between fossa navicularis and bulbar urethra
	Bulbar strictures	Starting at the penoscrotal junction and ending at the level of the urogenital diaphragm
	Penobulbar strictures	From penile urethra into the bulbar segment (compromising long segments of urethra)
Posterior urethra	Membranous urethral stenosis	Segment traversing the urogenital diaphragm, from proximal bulbar to distal verumontanum
	Prostatic urethral stenosis	Segment through the prostatic gland, starting at the proximal membranous urethra and extending to the bladder neck
	Bladder neck stenosis	Junction between the prostatic urethra and the bladder, requiring that the prostatic gland is in situ (ie, after TURP or simple prostatectomies)
	Vesicourethral anastomosis stenosis	Narrowing or obliteration at anastomotic site after radical prostatectomy

TURP = transurethral resection of the prostate.

Table 3 – EAU Urethral Stricture Guidelines Panel classification of male urethral stricture

Category	Description	Urethral lumen (Fr)	Degree
0	Normal urethra in imaging techniques		
1	Subclinical strictures	Urethral narrowing but ≥16 Fr	Low
2	Low-grade strictures	11–15 Fr	
3	High-grade or flow-significant strictures	4–10 Fr	High
4	Nearly obliterative strictures	1–3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

EAU = European Association of Urology.

Table 4 – EAU Urethral Stricture Guidelines Panel recommendations on perioperative management of male urethral strictures

Recommendations	Strength rating
Do not perform urethroplasty within 3 mo of any form of urethral manipulation.	Weak
Administer an intraoperative prophylactic regimen with antibiotics at the time of urethral surgery.	Strong
Remove the catheter within 72 h after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Perform first urethrography 7–10 d after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Strong

EAU = European Association of Urology.

in order to allow tissue recovery and stricture "maturation" before considering urethroplasty (Table 4). This improves the ability to identify the true extent of the fibrotic segments during subsequent surgery. If the patient develops incapacitating obstructive symptoms or urinary retention, an SPC should be inserted. Terlecki et al [30] proposed a diagnostic evaluation after 2 mo and urethroplasty after 3 mo of urethral rest. However, the optimal duration of urethral rest for all patients is not known, and the degree of associated infection and inflammation should be taken into account, with longer periods of rest in those contexts.

3.2. *Antibiotics*

For MUSD, antibiotic practices should be in accordance with the strong recommendations of the EAU guidelines on urological infections: (1) screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa, and (2) treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions.

An intraoperative prophylactic regimen with antibiotics (according to local antibiotic resistance profiles) is effective in reducing the rate of postoperative surgical site and UTI, both of which are contributors to failure of the repair [31]. Although most urologists continue with postoperative antibiotics upon and even beyond catheter removal, there is no evidence that such prolonged administration reduces the infective complication rate [31].

3.3. *Catheter management*

After uncomplicated endoluminal treatment, the catheter should be removed within 72 h [32].

After perineostomy or the first stage of staged urethroplasty, the catheter can be removed without need for urethrography after 3–5 d [33].

After one-stage urethroplasty and closure of the urethral plate after staged urethroplasty, urinary extravasation at the site of reconstruction must be avoided [34]. For this purpose, urinary diversion by either a transurethral catheter

Table 5 – EAU Urethral Stricture Guidelines Panel recommendations on follow-up after male urethroplasty

Recommendations	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong
Offer a routine follow-up of at least 1 yr after urethroplasty.	Strong
Adopt a risk-adjusted follow-up protocol.	Weak
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use PROM questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong

EAU = European Association of Urology; PROM = patient-reported outcome measure.

or an SPC with an urethral stent can be used. With respect to the type of catheter material, a prospective randomised (but underpowered) trial comparing silicone versus hydrogel-coated latex transurethral catheters showed no significant difference in the time to stricture recurrence or in the overall recurrence rate [34]. The size of the urethral catheter utilised usually varies between 14 and 20 Fr [35,36].

After urethroplasty, an indwelling catheter is commonly left in situ for 2–3 wk [36,37]. After 3 wk, an extravasation rate of 2.2–11.5% at urethrography has been reported after different types of urethroplasty [33,37,38]. However, success with early catheter removal has also been reported. After excision and primary anastomosis for noncomplicated anterior strictures, no significant difference was demonstrated in extravasation (6.8% vs 4.5%) and recurrence rates (4.9% vs 5.2%) between catheter removal at 1 or 2 wk, respectively [39]. Poelaert et al [35] reported an extravasation rate of 3.5% versus 8.3% when the catheter was removed $\leq$10 versus $>$10 d after all types of urethroplasty, but patients with catheterisation of $>$10 d had longer and more complex strictures.

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including periurethral inflammation, abscess formation, and fistulation [33,37]. Some authors have identified urinary extravasation as a predictive factor for stricture recurrence, especially with high-grade leaks (defined as length $\geq$1.03 cm and width $\geq$0.32 cm) [33,35]. In cases of persistent and significant urinary extravasation, the catheter should be maintained or reinserted and the examination repeated after 1 wk [37]. However, low-grade ("wisp like") extravasation does not appear to affect long-term restricture rate, and the catheter can be removed in these cases [33,40]. In case of any doubt about the significance of extravasation, it is safest to keep the catheter in for an additional week and redo the assessment.

Although there is no evidence that one imaging (pericatheter RUG and VCUG) modality is superior to the other, pericatheter RUG should be performed if there is a high risk of leakage, as it avoids the need for catheter reinsertion through a recently reconstructed urethra in case of a positive examination [33,40]. External clinical signs of impaired wound healing (eg, abscess formation and wound dehiscence) are also associated with a high risk (71.4%) of leakage [35].

4. Follow-up of male urethral strictures

4.1. *Rationale for follow-up after urethral surgery*

The rationale is to detect and manage any complication or recurrence (Table 5). Up to 54% of patients after anterior urethroplasty [41] would present with complications with short to medium follow-up. Though urethroplasty provides the highest chances for patency, some patients will experience recurrence [42].

4.2. *Definition of success after urethroplasty surgery*

The "traditional academic" definition of success after urethroplasty has been considered as the lack of any postoperative intervention for restricture [43]. This definition is problematic as it ignores asymptomatic or even symptomatic recurrences with patients not willing to undergo further surgeries [43].

A more objective definition is the "anatomic success", considered as normal urethral lumen during RUG or cystoscopy, regardless of patient symptoms. Stricture recurrence or anatomical failure is considered by some groups as urethral narrowing found to be endoscopically impassable—without force—using a 16F flexible endoscope [19]. This definition is stricter, as up to 35% of cystoscopic recurrences after bulbar urethroplasty remain asymptomatic and thus would have been considered successful if a "traditional" definition was used [19]. Not all anatomic recurrent strictures would need further treatment, and intervention is suggested when associated with recurrence of symptoms, stricture-related high PVRs, or a stricture calibre of $<$14F—even if the two latter ones are asymptomatic [43].

In contemporary practice, evaluation of urethral surgery outcomes has shifted towards a "patient-reported definition of success". The aim of any urethral intervention is to allow patients to return to a normal state of voiding whilst maintaining quality of life or to minimise symptoms, reduce disability, and improve health-related quality of life by restoring normal urinary function [44]. Even if the surgeon has reconstructed a wide and patent urethra, if patients experience complications or perceive their urinary function as not improved, they will not rate their outcome as successful [43]. Table 6 summarises known predictors for dissatisfaction after urethral surgery. Kessler et al [45]

Table 6 – Predictors of patient dissatisfaction after urethral surgery

Predictor/symptoms	Measure of effect
Weak/very weak urinary stream [45]	NR
Penile curvature [45]	NR
Penile shortening [45]	NR
Worsening of erectile function [45]	NR
Impairment of sexual life [45]	NR
Sexual activity alteration [61]	OR4.36(1.54–12.37) *
Erection confidence (SHIM) [61]	OR1.53(1.12–2.07) *
Inability to ejaculate (MSHQ) [61]	OR1.52(1.15–2.01) *
Urethral pain [61]	OR1.71(1.05–2.77) *
Bladder pain [61]	OR2.74(1.12–6.69) *
Urinary strain (CLSS) [61]	OR3.23(1.74–6.01) *
Hesitancy (IPSS) [61]	OR2.01(1.29–3.13) *
Voiding quality of life (IPSS) [61]	OR1.96(1.42–2.72) *
Penile shortening [55]	OR2.26(1.39–3.69) **
Chordee [55]	2.26(1.44–4.19) **

CLSS = Core Lower Urinary Tract Symptom Score; IPSS = International Prostate Symptoms Score; MSHQ = Male Sexual Health Questionnaire; NR = not reported, but statistically significant; SHIM = Sexual Health Inventory for Men.
* $p < 0.05$.
** $p < 0.001$.

reported that only 78.3% of patients with clinical success described themselves as (very) satisfied, whilst 80% of clinical failures considered themselves as (very) satisfied with their outcomes. Owing to this evident discrepancy between surgeon's and patient's assessments, PROMs have been developed for the follow-up after urethroplasty [9,44].

A logical and practical approach for urethral surgery outcomes would combine both anatomic (endoscopic) and patient-reported success [43]. As a panel, we suggest using a functional definition of success for its use in clinical practice, namely, a lack of symptoms and/or no need for further interventions. Collection also of objective anatomic outcomes would be for academic purposes, in order to allow a comparison of surgical outcomes among reconstructive urological surgeons and centres. Objective and subjective outcome measures should be assessed and reported simultaneously, but separately, when evaluating urethroplasty results [43].

5. Follow-up tools

5.1. Diagnostic tools

5.1.1. Calibration

The difference between calibration and urethral dilation is usually subjective as soft strictures may be dilated during calibration [46]. Therefore, urethral calibration should be used with caution for follow-up after urethroplasty.

5.1.2. Urethrocystoscopy

Flexible urethrocystoscopy has been considered the most useful tool to confirm the presence or absence of a recurrent stricture [47,48]. In addition, it could be a measure to calibrate the lumen, bearing in mind the most commonly used endoscopes: 15.7F (5 mm diameter) or 17.3F (5.5 mm diameter) [48]. Urethrocystoscopy allows differentiation of recurrences as diaphragm/cross-bridging, which responds to single simple interventions or significant urethral restricture that requires repeated interventions or redo reconstructive surgery [49]. Endoscopic assessment at 3 mo after anterior urethroplasty can predict the risk for further reintervention at 1 yr [47]. The main problem with using urethrocystoscopy for routine follow-up is the low compliance of patients—only 54% underwent endoscopy at 1 yr after urethroplasty [19].

5.1.3. RUG and VCUG

RUG combined with VCUG are commonly used to confirm suspected recurrence [50] or as part of a routine protocol to assess postoperative urethral patency [51].

5.1.4. Urethral ultrasound—SUG

The use of SUG as a follow-up tool is not very common. It would be a reliable tool for diagnostic recurrent strictures [50].

5.2. Screening tools

These tools are used to assess whether there is suspicion of stricture recurrence and need for subsequent diagnostic evaluation (see section 1).

5.2.1. Flow-rate analysis

Evaluating the Q_{max} is the commonest follow-up tool. Different cut-off points from Q_{max} 15 or 12 ml/s were suggested to consider the intervention as failure or to trigger confirmatory test for recurrence. There is no clear threshold, and 19% of patients with Q_{max} <14 ml/s would still have a patent urethra, allowing passage of a 15F cystoscope [52]. A comparison of both pre- and postoperative Q_{max} levels was suggested, and a difference in Q_{max} of $\leq$10 ml/s is found to be a reliable screen tool for recurrence—sensitivity 92% and specificity 78% [51]. Unfortunately, this improvement after urethroplasty is significantly different between age groups [53]. Another parameter to consider is the shape of the voiding curve, recording it as flat (obstructed) or bell shaped [54]. An obstructive voiding curve demonstrated 93% sensitivity to predict recurrent strictures, whilst a combination of urinary symptoms and obstructive voiding curve achieved 99% sensitivity and 99% negative predictive value [54].

5.2.2. PVR ultrasound measure

PVR ultrasound measure is significantly increased in patients with recurrent strictures compared with those without recurrences [50], but currently there is no literature support for its solo use to assess urethral stricture recurrence.

5.2.3. Symptoms questionnaires

The International Prostate Symptoms Score (IPSS) showed significant improvement after successful urethroplasty and inverse significant correlation with Q_{max} [55]. The mean improvement of IPSS is around –11 points (range –19 to –5) [53]. A combination of IPSS and Q_{max} analysis was suggested

to diagnose recurrences. The use of an IPSS cut-off of 10 points associated with Q_{max} >15 ml/s would prevent further invasive studies in 34% of patients, whilst only 4.3% of strictures <14 F would have been missed. The use of an IPSS cut-off of 15 points associated with Q_{max} >15 ml/s would prevent further invasive studies in 37% of cases, whilst 6% of strictures <14 F would have been missed [56].

5.2.4. *Quality of life assessment using disease-specific questionnaires*

The USS-PROM [9,44] has been found to be useful for assessing outcomes in anterior urethroplasty patients [44]. PROM questionnaires should be implemented in each visit, as they are likely to improve, to check for functional success. Sexual function including erectile and ejaculatory functions should be evaluated by validated tools if not assessed in a condition-specific PROM.

6. Ideal interval and length of follow-up

The optimal follow-up strategy must allow for an objective determination of anatomic and functional outcomes to assess surgical success, whilst avoiding excessive invasive testing that leads to unnecessary cost, discomfort, anxiety, and risk [43].

After anterior urethroplasty, 21% of recurrences are clinically evident, and cystoscopically confirmed, after 3 mo [57] and 96% after 1 yr [49]. Of bulbar stricture recurrences, 23% would be detected during the 2nd year of follow-up and the percentage of recurrences would decrease thereafter [42].

Early recurrences are more frequent in patients with LS/balanitis xerotica obliterans (BXO) and older age, in longer strictures and when skin grafts were used [57]. Late recurrences (>5 yr after urethroplasty) could be observed

(A) Surgeries with low-risk of recurrence

- Anastomotic urethroplasties in the bulbar/(bulbo)membranous segment with no history of radiotherapy, hypospadias or BXO/LS features

	3 mo	12 mo	24 mo [a]
Uroflow	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation (urethrocystoscopy/RUG-VCUG)	+ [b]	On indication	On indication

(B) Surgeries with standard risk of recurrence

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias, or BXO/LS features
- Penile urethroplasties
- Nontraumatic posterior urethroplasties
- Graft or/and flap—substitution—urethroplasties

	3 mo	12 mo	24 mo	5 yr [c]
Uroflow	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation (urethrocystoscopy/RUG-VCUG)	+	+	+	On indication

Fig. 2 – EAU Urethral Stricture Guidelines Panel follow-up protocol proposal after male urethroplasty: (A) surgeries with a low risk of recurrence and (B) surgeries with standard risk of recurrence.
EAU = European Association of Urology; BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient-reported outcome measures; RUG = retrograde urethrogram; VCUG = voiding cystourethrography.
[a]Follow-up could be discontinued after 2 yr, advising the patient to seek for urological evaluation if symptoms worsened. Academic centres could increase the length of follow-up for research purposes.
[b]The panel suggests performing an anatomic assessment at 3 mo.
[c]Follow-up could be discontinued after 5 yr, advising the patient to seek for urological evaluation if symptoms worsened. A longer follow-up period should be considered after penile and substitution urethroplasties. Academic centres could increase the length of follow-up for research purposes.

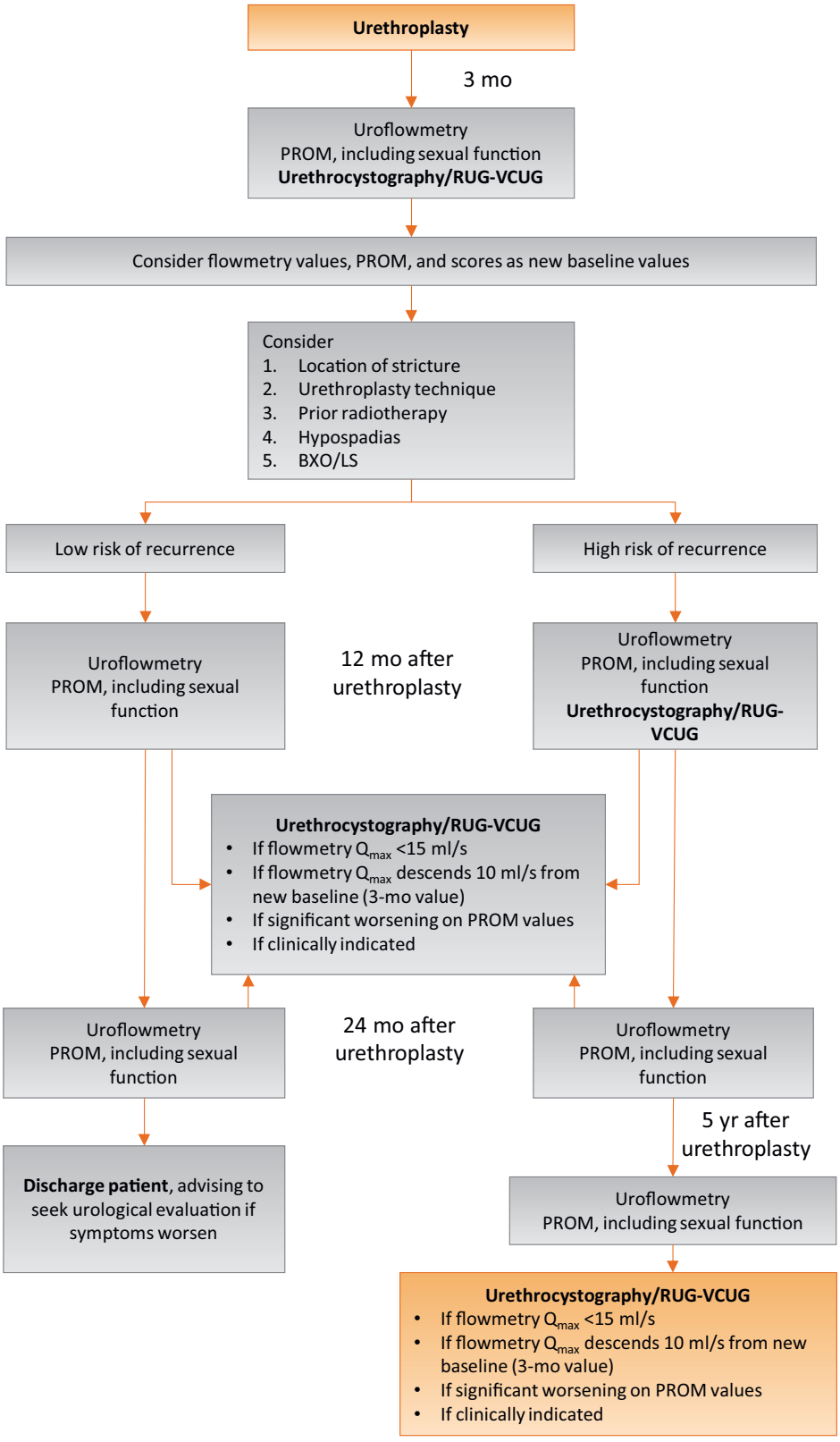

Fig. 3 – Follow-up after urethroplasty.
BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient-reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

in up to 15% of cases [42,52]. These appear mainly after substitution urethroplasties, especially the ones using skin as graft. Certainly, patients should be instructed to seek urological evaluation if they experience late recurrence symptoms [58]. Long-term follow-up could be offered in academic institutions, to provide detailed information of outcomes in particular contexts (Fig. 2-3).

7. Risk-stratified proposals

As the risk of recurrence and side effects are related to the type of stricture and urethroplasty, a different follow-up schedule was proposed based upon risk stratification. This was shown to be cost effective, potentially saving up to 85% of costs at 5 yr [59]. If evidence of good anatomical outcome is obtained using cystourethroscopy or RUG/VCUG at 3–6 mo postoperatively, flowmetry and questionnaires should be considered as the new baseline. Thereafter, follow-up could be performed safely with noninvasive tests. Any significant decline (25–30%) in Q_{max} or $Q_{max} - Q_{ave}$ should be investigated further with cystourethroscopy, even in patients who are symptom free [43,60]. Routine cystourethroscopy at 12–15 mo should be performed at the surgeon's discretion, based on the presence of any the following three factors: higher-risk patients, evidence of partial narrowing at 3-mo assessment, and low-volume surgeons [43].

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Study concept and design: Campos-Juanatey, Osman, Greenwell, Martins, Riechardt, Waterloos, Barratt, Chan, Esperto, Ploumidis, Verla, Dimitropoulos, Lumen.
Acquisition of data: Lumen, Campos-Juanatey, Greenwell, Martins, Osman, Riechardt, Waterloos, Barratt, Chan, Esperto, Ploumidis, Verla, Dimitropoulos.
Analysis and interpretation of data: Lumen, Campos-Juanatey, Greenwell, Martins, Osman, Riechardt, Waterloos, Barratt, Chan, Esperto, Ploumidis, Verla, Dimitropoulos.
Drafting of the manuscript: Campos-Juanatey, Osman, Greenwell, Martins, Riechardt, Waterloos, Barratt, Chan, Esperto, Ploumidis, Verla, Dimitropoulos, Lumen.
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Surgery in Motion

Hood Technique for Robotic Radical Prostatectomy—Preserving Periurethral Anatomical Structures in the Space of Retzius and Sparing the Pouch of Douglas, Enabling Early Return of Continence Without Compromising Surgical Margin Rates

Vinayak G. Wagaskar[a,*], *Ankur Mittal*[b], *Stanislaw Sobotka*[a], *Parita Ratnani*[a], *Anna Lantz*[a], *Ugo Giovanni Falagario*[a], *Alberto Martini*[a], *Zach Dovey*[a], *Patrick-Julien Treacy*[a], *Prachee Pathak*[a], *Suit Nair*[a], *Berryhill Roy*[a], *Dimple Chakravarty*[a], *Sara Lewis*[c], *Kenneth Haines III*[d], *Peter Wiklund*[a], *Ash Tewari*[a]

[a] *Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA;* [b] *Department of Urology, All India Institute of Medical Sciences, Rishikesh, India;* [c] *Department of Radiology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA;* [d] *Department of Pathology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA*

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Abstract

Background: A common side effect following radical prostatectomy is urinary incontinence. Here, we describe a novel surgical technique to reduce postoperative urinary incontinence and facilitate early return of continence.
Objective: To describe the novel "hood technique" for robotic-assisted radical prostatectomy (RARP).
Design, setting, and participants: This is an institutional review board–approved prospective study of 300 patients (median age 64 yr) with localized prostate cancer treated with the RARP hood technique at a major urban hospital between April 2018 and March 2019. The exclusion criteria were as follows: patients with anterior tumor location based on biopsy or multiparametric magnetic resonance imaging. All but one patient participated in follow-up over 12 mo after the procedure.
Surgical procedure: The RARP "hood technique" was performed to preserve the detrusor apron, puboprostatic ligament complex, arcus tendineus, endopelvic fascia, and pouch of Douglas.
Measurements: Clinical data collected included pre- and intraoperative variables, and postoperative functional and oncological outcomes and complications. Descriptive statistical analysis was performed.
Results and limitations: Continence rates at 1, 2, 4, 6 12, 24, and 48 wk after catheter removal were 21%, 36%, 83%, 88%, 91%, 94%, and 95%, respectively. Positive surgical margin rate was 6%. Thirty patients (9.7%) experienced complications after RARP: 17 (5.7%), 11 (3.6%), and one (0.4%) had Clavien-Dindo grade I, II, and III complications, respectively. This study was conducted within a single health system and may not be generalizable. The study lacked randomization and a comparative arm.

* Corresponding author. Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, 1425?Madison Avenue, New York, NY 10029, USA. Tel.: +1 9293702225; Fax: +1 6465378508.
E-mail address: Vinayak.wagaskar@mountsinai.org (V.G. Wagaskar).

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Conclusions: Results indicate that the hood technique spares musculofascial structures anterior to the urethral sphincter complex with early return of continence after surgery, without compromising positive surgical margin rates. Exclusion of anterior tumor location contributed to a reduction in positive surgical margins.
Patient summary: By better preservation of anatomical structures around the urethra, we were able to achieve early return of urinary continence without a negative impact on complications and cancer outcomes.
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1. Introduction

Prostate cancer is commonly treated with robotic-assisted radical prostatectomy (RARP). This technique is challenging given the need to address the competing goals of cancer control, maintenance of urinary continence, and recovery of sexual function. While oncological efficacy is the most critical endpoint, quality of life issues impact survivorship and are important considerations in this surgery. The major side effects of RARP are sexual dysfunction and urinary incontinence. The latter, in particular, can have a significant negative impact [1] on day-to-day life and is the focus of this study.

Continence following radical prostatectomy is achieved through the delicate and well-orchestrated interplay between (1) groups of muscles (smooth and voluntary) that are (2) anchored to fixed bony (public symphysis) and ligamentous structures (puboprostatic ligaments and arcus tendineus) [2] and (3) complemented by the cushioning effect of mucosa (urethra) and the surrounding soft and fascial tissue (lateral prostatic fascia and detrusor apron) [3], intact innervation [2], angulation between the bladder neck and urethra [4], and full functional length urethra preservation [5], which also helps in recovery of continence.

There have been a number of modifications in, and refinements to, surgical techniques to optimize continence after RARP. These include modifications in apical dissection to maximize urethral length [6], preservation of the anterior puboprostatic complex (anterior reconstruction) [7], suturing of Denonvilliers' fascia for posterior support (posterior reconstruction and Rocco stitch) [8], bladder neck plication [9], use of suspension sutures, wrapping of the detrusor behind the anastomosis (detrusor wrap) [10,11], and combinations of these strategies.

Secco et al [12] developed a novel anterior-posterior modification to RARP to preserve structures in the space of Retzius (anterior support and detrusor apron). This technique preserves the entire space of Retzius and its contents by approaching the prostate and the bladder neck through the pouch of Douglas. There are convincing data describing the impact of this technique on the early return of continence. Despite considerable enthusiasm for this strategy, many more surgeons perform robotic prostatectomy from the anterior aspect (with approximately 1 million such surgeries performed [13–16]) than through the anterior-posterior approach.

Inspired by the work of Dr. Robert Myers, we conceptualized a novel surgical technique that preserves the contents of the space of Retzius using an anterior approach. With our novel technique, preserved tissue after prostate removal has the appearance of a "hood" comprising the detrusor apron, arcus tendineus, puboprostatic ligament, anterior vessels, and some fibers of the detrusor muscle. This hood surrounds and safeguards the membranous urethra, external sphincter, and supportive structures (Fig. 1).

Our primary aim is to describe surgical steps of the novel "hood technique". The secondary aim of this study is to present early continence outcomes, complications, and surgical margin rates of the hood technique. In this study, we have also identified periurethral structures in preoperative multiparametric magnetic resonance imaging. Additionally, we reviewed continence outcomes of the hood technique, a previously published technique by a senior author (A.K.T.), and published results of the Retzius-sparing approach.

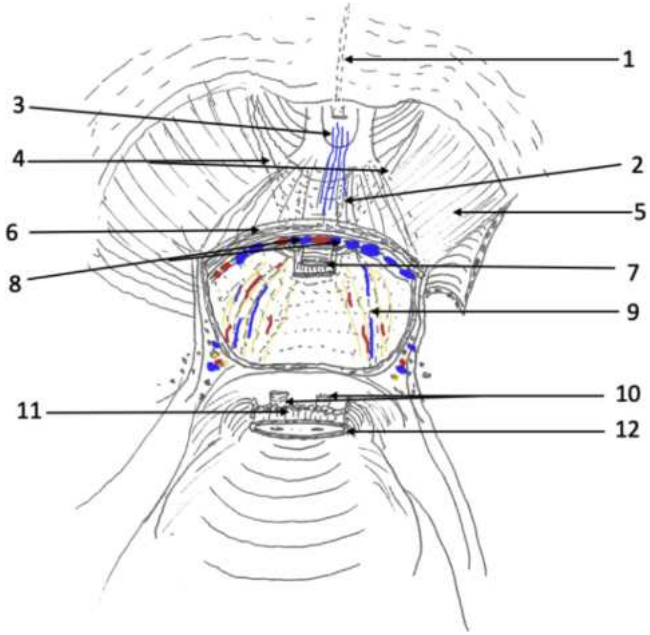

Fig. 1 – Sketch demonstrating hood surgical anatomy. Anatomical components of the hood surround and safeguard the membranous urethra and the external urethral sphincter, and thereby urethrovesical anastomosis. 1 = pubic symphysis; 2 = external urethral sphincter; 3 = superficial venous layer; 4 = puboperinealis muscle; 5 = levator ani muscle; 6 = detrusor apron; 7 = urethral stump; 8 = deep venous complex; 9 = neural hammock; 10 = vas deferens; 11 = retrotrigonal layer; 12 = bladder neck.

2. Patients and methods

2.1. Anatomical foundations of the hood technique

We performed a nonsystematic literature review of relevant studies on anatomical structures in the space of Retzius (ie, anterior fibromuscular stroma, prostatic capsule, detrusor apron, and venous plexus, arteries, and nerves). To identify these structures, immunohistochemical staining was performed on the entire anterior tissue of patients who had undergone conventional radical prostatectomy with the help of an expert genitourinary pathologist (K.H. III). Masson's trichrome staining was used to identify elastin, collagen, smooth and striated muscle, and vessels [17], and S-100 staining was used to confirm the presence of nerves [18] (Fig. 2). Additionally, we identified and annotated these "hood" components on MRI to better understand their relationship with the sphincter and the prostate (Fig. 2).

2.1.1. Puboprostatic ligamentous complex

The puboprostatic ligamentous complex comprises the puboprostatic ligaments, arcus tendineus (Fig. 3), and puboperinealis muscle (Figs. 3 and 4). The arcus tendineus is the lateral condensation of endopelvic fascia that extends from puboprostatic ligaments to the ischial spine. These ligaments are the dense pyramid-shaped medial portions of the distal endopelvic fascia. Puboprostatic ligaments fix the bladder, prostate, and membranous urethra to the pubic symphysis (Fig. 3) [6]. The puboperinealis is a paired muscle that originates from the pubis, flanks the prostatic-urethral junction, and ultimately terminates at the perineal body. This muscle acts as a "hammock" supporting the urethra posteriorly and is responsible for the quick-stop phenomenon of urination.

2.1.2. Detrusor apron

The detrusor apron is a tissue that partially obscures the prostate and is thought to be an extension of the anterior wall of the bladder beyond the bladder neck (Figs. 2 and 3) [3]. Figure 2 shows a slide section of the detrusor apron and prostate of a patient who underwent RARP without preservation of the detrusor apron confirming the presence of smooth muscles, skeletal muscles, and nerves.

2.2. Surgical techniques

A four-arm da Vinci Xi Surgical System (Intuitive Surgical-ISRG, Sunnyvale, CA, USA) was used for all cases. All RARPs were performed by a single experienced surgeon (A.K.T.) at least 6 wk after prostate biopsy.

2.2.1. Patient positioning and port placement

The patient is placed in the steep Trendelenberg position. Six laparoscopic trocars are placed as previously published [19].

2.2.2. Development of the retropubic space

Using a camera lens with 0° optic, the peritoneum is incised with an inverted U-shaped incision to expose the bladder and the anterior prostate without exposing puboprostatic ligaments after removing overlying fat tissues.

2.2.3. Bladder neck dissection

The bladder neck is incised and deepened till the Foley catheter is seen. We then developed a plane behind the posterior wall of the bladder neck that exposed a consistent fibromuscular layer, which we call "the retro trigonal layer."

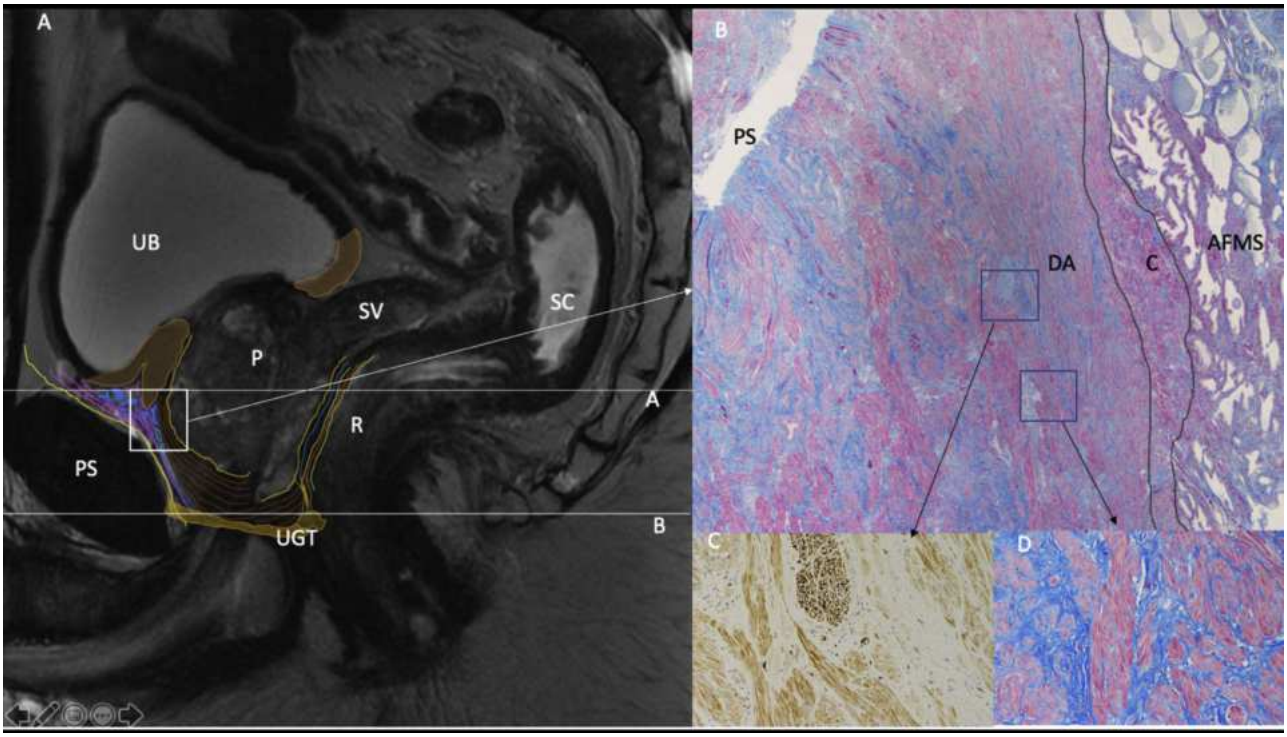

Fig. 2 – (A) Annotated multiparametric magnetic resonance imaging (mpMRI) of the pelvis (sagittal section) outlining the bladder neck, prostate capsule, fascial layers, and muscles around the prostate and urogenital diaphragm. Sections A and B pass from the midgland of the prostate and external urethral sphincter, respectively. (B) Hematoxylin and eosin staining of the portion shown in Figure 2A. From right to left, anterior fibromuscular stroma of the prostate (AFMS), layer of small veins and arteries suggesting the capsule of the prostate (C), layers of muscle fibers and nerves demonstrating detrusor apron (DA), and pubic symphysis (PS). (C) S-100 staining of the portion shown in Figure 2B, confirming the presence of nerve. (D) Masson's trichrome staining of the portion shown in Figure 2B, confirming the presence of smooth muscles. P = prostate; PS = pubic symphysis; R = rectum; SC = sigmoid colon; SV = seminal vesicle; UB = urinary bladder; UGT = urogenital diaphragm.

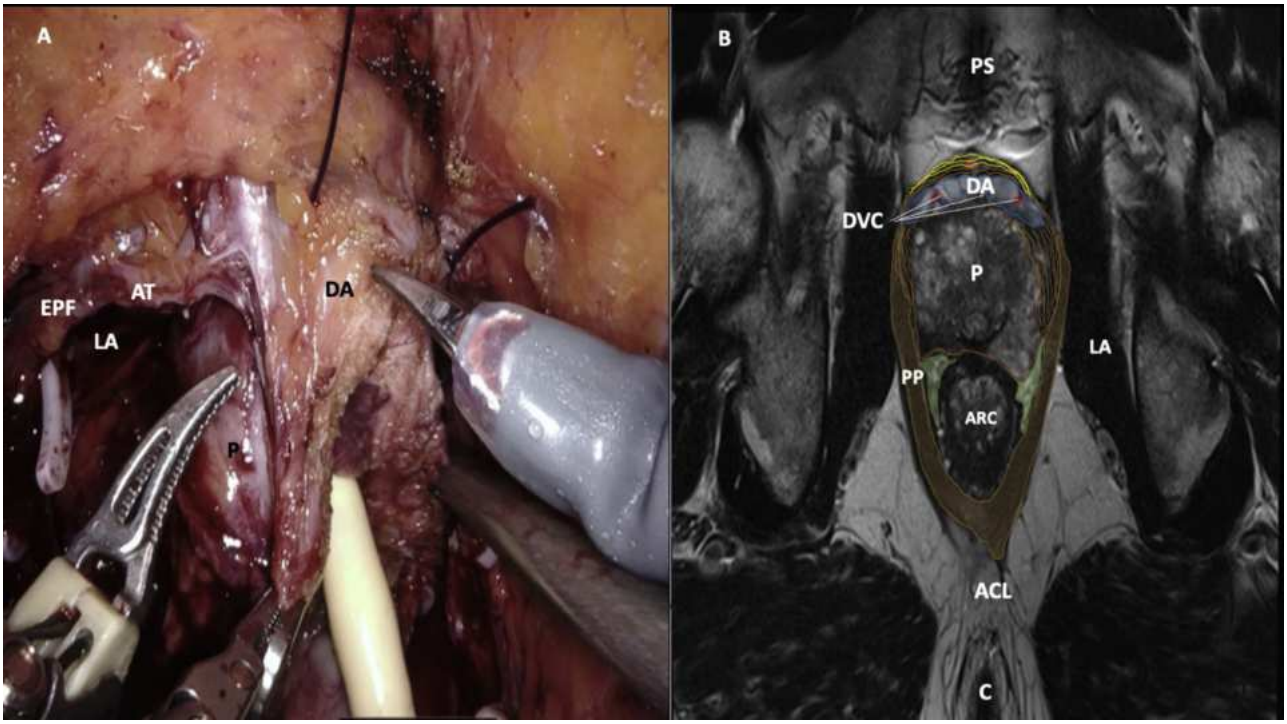

Fig. 3 – MRI and intraoperative images corresponding to section A. (A) Intraoperative image showing components of the hood. (B) MRI of the pelvis (cross section) corresponding to the intraoperative image. ACL = anococcygeal ligament; ARC = anorectal canal; AT = arcus tendineus; C = coccyx; DA = detrusor apron; DVC = deep venous complex; EPF = endopelvic fascia; LA = levator ani; MRI = magnetic resonance imaging; P = prostate; PP = puboperinealis muscle; PS = pubic symphysis.

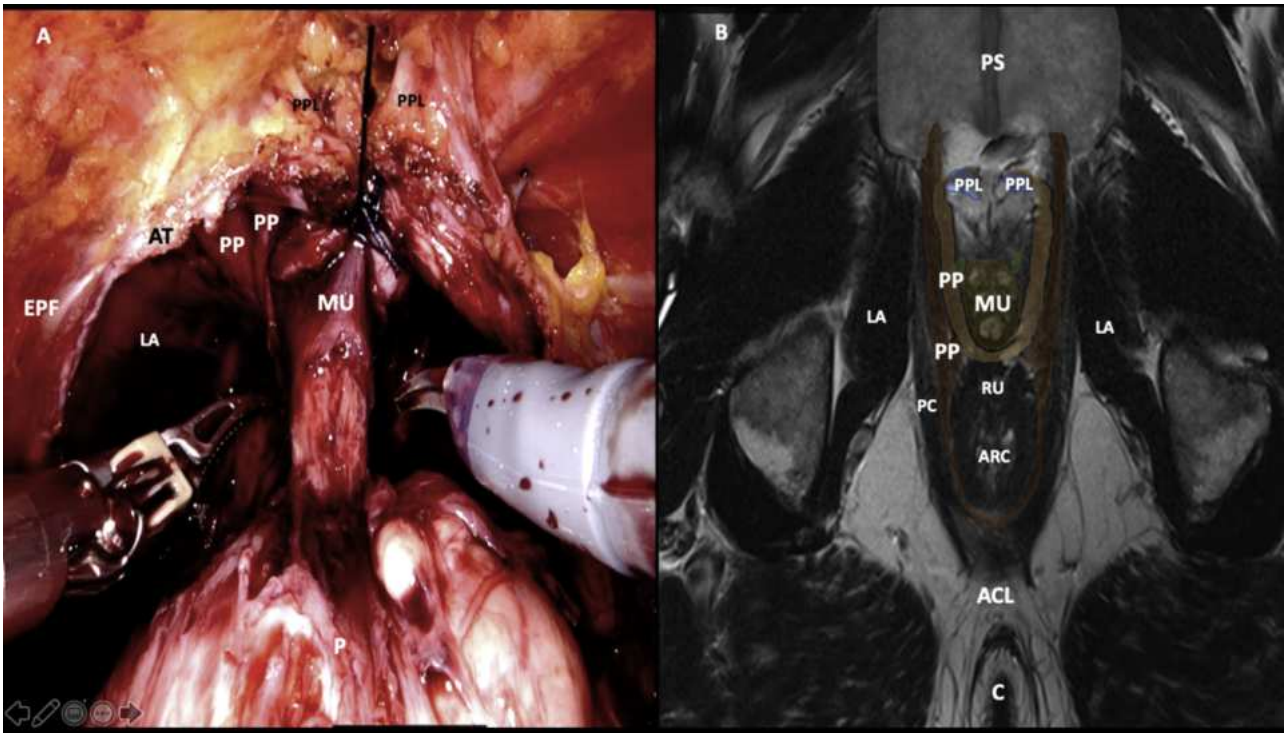

Fig. 4 – MRI and intraoperative images corresponding to section B. (A) Intraoperative image showing the membranous urethra and muscles surrounding the urethral sphincter. (B) MRI of the pelvis (cross section) corresponding to the intraoperative image. ACL = anococcygeal ligament; ARC = anorectal canal; AT = arcus tendineus; C = coccyx; EPF = endopelvic fascia; LA = levator ani; MRI = magnetic resonance imaging; MU = membranous urethra; PC = prostatic capsule; PP = puboperinealis muscle; PPL = puboprostatic ligaments; PS = pubic symphysis; RU = rectourethralis muscle.

2.2.4. Vas deferens and seminal vesicle dissection

The vas deferens is isolated one at a time, dissected out using an athermal technique, and cut. We then developed a plane between the seminal vesicles and the surrounding fascia, which we term the "the median avascular plane."

2.2.5. Lateral pedicle control

A plane is developed between the prostatic capsule and Denonvilliers' fascia athermally by a combination of sharp and blunt dissection, proceeding distally toward the apex and laterally on either side. We incise endopelvic fascia (not shown in video) when we do not attempt nerve sparing. Then, we come to the lateral attachments where the perforating arteries are entering into the prostatic capsule. We sharply cut them, and develop a plane between the capsule and the medial aspect of the pedicular vessels. They are sharply cut after being secured by Hem-o-lock clips.

2.2.6. Circumferential apical dissection

The prostate is retracted to one side, and anterolateral dissection is performed with the goal of preserving the urethral sphincter.

2.2.7. Control of dorsal venous complex

The dorsal venous complex is ligated using 2-0 Vicryl suture in continuous fashion.

2.2.8. Development of hood and urethral transection

A plane was developed between the detrusor apron and the anterior fibromuscular layer of the prostate till the prostatic apex. The anterior urethra was cut sharply and the prostate was freed.

2.2.9. Total anatomical reconstruction technique and anastomosis

The first step of posterior reconstruction was developing "mattress" for anastomosis using V-lock suture. This mattress comprised the Denonvilliers' musculofascial plate and the posterior bladder neck. Two-layer bladder neck reconstruction was performed thereafter using V-lock suture. Urethrovesical anastomosis was performed using barbed suture. Arcus tendineus is sutured to partial thickness bites of the detrusor muscle.

2.3. Surgical outcomes

2.3.1. Study population

We reviewed our prospectively maintained radical prostatectomy database to retrieve the records of patients who underwent the hood technique for RARP from April 1, 2018 to March 15, 2019, performed by a single experienced prostate cancer surgeon (A.K.T.). Patients whose biopsy was positive at the anterior prostate ($n = 27$) or whose preoperative MRI showed an anterior prostatic lesion ($n = 20$) were excluded from undergoing the hood technique. Patients who had received prior hormonal or radiotherapy for prostate cancer were excluded from the analysis. Pelvic lymph node dissection (PLND) was performed in patients with Gleason score $\geq 3+4$. Limited PLND (obturator lymph nodes on both sides) was performed in Gleason score 7 patients, and extended PLND (includes the common iliac, external iliac, internal iliac, and obturator group of lymph nodes on both sides) was performed in patients with Gleason score $\geq 4+4$. This study was approved by the institutional review board (IRB-19-01888).

2.3.2. Outcome measures and statistical analysis

Intraoperative data included console time, total operative duration, nerve sparing, intraoperative frozen section results, and intraoperative blood loss or need for transfusion. Postoperative variables included days of catheterization, complications, pathological stage, and continence status.

Patients were followed up at 6, 12, 24, 36, and 48 wk after catheter removal as part of standard postoperative protocol for continence status and the status of oncological outcome. Additional third-party telephone interviews were conducted by a urological fellow (V.G.W.) to determine early continence at 1, 2, and 4 wk. Patients were considered continent if they were pad free all the time. Continence data have been verified independently by two coauthors (U.F. and P.T.).

Descriptive techniques were performed for the overall study population. Continuous variables were reported as median and interquartile range (IQR). Categorical variables were reported as rates. Variables were entered into a custom-designed database in Microsoft Excel for Mac version 16.35. Data analysis was performed using Statistical Analysis Software version 9.4 (SAS v.9.4).

Table 1 – Demographic and preoperative characteristics of the study population

Variables	Overall population ($n = 300$)
Age (yr), median (IQR)	64 (58, 68)
BMI (kg/m^2), median (IQR)	27 (25, 29)
Prostate volume (ml), median (IQR)	51 (40, 64)
IPSS, median (IQR)	
Questions 1–7	8 (4, 14)
Question 8	2 (1, 3)
IIEF, median (IQR)	57 (35, 67)
PSA (ng/mL), median (IQR)	5.7 (4.5, 8)
PSA density (ng/mL^2), median (IQR)	0.12 (0.09, 0.16)
Clinical T stage, *n* (%)	
T1	153 (51)
T2	104 (35)
T3	43 (14)
Biopsy Gleason score, *n* (%)	
3 + 3	47 (15.6)
3 + 4	121 (40.4)
4 + 3	75 (25.0)
4 + 4	39 (13)
>4 + 4	18 (6)
Risk assessment CAPRA score, *n* (%)	
Low	35 (11.6)
Intermediate	198 (66)
High	67 (22.4)

BMI = body mass index; CAPRA = Cancer of the Prostate Risk Assessment; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; PSA = prostate-specific antigen.

3. Results

Three hundred patients were included in the analysis. Preoperative characteristics of the study population are summarized in Table 1. The median age at the time of surgery was 64 yr (IQR 58, 68) and the median body mass index was 27.2 kg/m^2 (IQR 25.2, 29.5). The median prostate-specific antigen level was 5.7 ng/mL (4.5, 8). Table 2 summarizes patients' intra- and postoperative characteristics. The median operative duration was 169 min, while the median console duration was 118.5 min. Preoperative prostate biopsies for these patients were as follows: 47 (16%), 121 (40%), 75 (25%), 39 (13%), and 18 (6%) had Gleason scores of 3 + 3, 3 + 4, 4 + 3, 4 + 4, and >4 + 4, respectively. The median number of lymph nodes removed in limited PLND was 7 (IQR 4, 8), while it was 21 (IQR 16, 23) in extended PLND.

Table 2 – Intraoperative outcomes and surgical pathology

Variables	Overall population (n = 300)
Console time (min)	118.5 (100, 141)
Total surgery time (min)	169 (147, 195)
Nerve sparing, n (%)	
Bilateral	240 (80)
Monolateral	42 (14)
Non–nerve sparing	18 (6)
Final pathological stage	
pT2	244 (81.3)
pT3	56 (18.7)
Lymph node	
N0	286 (95.3)
N1	14 (4.7)
Surgical margins	
Negative	282 (94)
Positive	18 (6)
Neurosafe (frozen section) positive	8 (2.7)
Final pathology positive	10 (3.3)

Table 3 – Surgical complications after RARP (n = 299)

Complications	n (%)	Clavien-Dindo grade
None	270 (90.3)	
Intraoperative bowel injury	0	
Intraoperative ureteric injury	0	
Pulmonary embolism	0	
Acute urinary retentions (necessitating recatheterization)	7 (2.3)	IIIa
Anastomotic urine leakage	0	
Lymphocele requiring drainage	0	
Wound infection	0	
Urinary tract infection	17 (5.7)	II
Meatal stenosis	4 (1.3)	IIIa
Anastomotic stricture	0	
Incisional hernia (elective repair)	1 (0.4)	IIIb

RARP = robotic-assisted radical prostatectomy.

3.1. Surgical complications

Table 3 shows a comprehensive list of surgical complications. No intraoperative complications (eg, bowel or ureteric injury) were seen. Seven patients experienced acute urinary retention after catheter removal. These patients required recatheterization (Clavien-Dindo grade IIIa) and had successful trial of void after 7 d. One patient developed an incisional hernia from the epigastric extraction site that required subsequent repair (Clavien-Dindo grade IIIb). Seventeen patients developed urinary tract infections, all of whom required antibiotics (Clavien-Dindo grad II). Four patients developed meatal stenosis and required a urethral dilation procedure under lubrication (Clavien-Dindo grade IIIa).

3.2. Continence outcomes

Catheter removal is performed on postoperative day 7. The continence rate (defined as completely pad free) at the 1st week after catheter removal was 62/300 (21%) and gradually improved to 109/300 (36%) by the 2nd week.

Table 4 – Continence outcomes per week (pads per day)

Week	N	0 Pad	1 Pad	2 Pads	3 Pads	4 Pads	≥5 Pads
Week 1	300	62 (20.7)	127 (42.3)	48 (16)	31 (10.3)	22 (7.3)	10 (3.3)
Week 2	300	109 (36.3)	97 (32.3)	57 (19)	23 (7.7)	8 (2.7)	6 (2)
Week 4	300	249 (83)	12 (4)	18 (6)	17 (5.7)	3 (1)	1 (0.3)
Week 6	300	265 (88.3)	9 (3)	17 (5.7)	6 (2)	2 (0.7)	1 (0.3)
Week 7	299	273 (91)	10 (3.3)	10 (3.3)	4 (1.3)	1 (0.3)	1 (0.3)
Week 24	299	282 (94)	9 (3)	6 (2)	1 (0.3)	1 (0.3)	0 (0.0)
Week 48	299	286 (95.3)	9 (3)	3 (1)	1 (0.3)	0 (0.0)	0 (0.0)

Continence rates continued to improve at 4 wk (249/300, 83%), 6 wk (265/300, 88%), 12 wk (274/300, 91%), 24 wk (282/300, 94%), and 48 wk (286/300, 95%) after catheter removal. Fourteen patients (5%) were not continent at the end of 12-mo follow-up. Of these patients, nine were using an occasional one pad per day (PPD), three patients were using 2 PPDs, and one patient was using four PPDs. One patient was lost to follow-up 12 wk after prostatectomy. Four of the patients using two or more PPDs developed urinary tract infections after prostatectomy. Three of these patients received biofeedback training at 12 wk after prostatectomy. The remaining patient (using four PPDs) declined biofeedback and considered pharmacotherapy for incontinence (Table 4).

4. Discussion

Radical prostatectomy is the reference standard for the treatment of localized prostate cancer. This technique has been modified and refined over many years. Nevertheless, the procedure continues to have several common side effects, including urinary incontinence, which can significantly impact the quality of life for prostate cancer survivors and which is the focus of this study. The hood technique for robotic-assisted prostatectomy described in this study represents a modification to the anterior approach similar to previously published techniques, such as PERUSIA technique [20] and the technique by de Carvalho et al [21] that preserves the musculofascial structures anterior the prostate. This principle of anterior structure preservation had been used in open retropubic radical prostatectomy as well [22]. Our study shows that the hood technique confers three key benefits: early continence, a low positive surgical margin rate, and the ability to visualize anatomical landmarks.

Beyond the goal of long-term urinary continence, attaining early continence after RARP has also been both desirable and challenging. To address this concern, Galfano et al [23] first introduced Bocciardi's Retzius-sparing approach in 2013 with a 1-wk continence rate of 75% (Fig. 5). While the 1-wk continence rate with the hood approach was 21% in our study, the continence rate at 3 mo was 91%, higher than our previously reported outcomes [19]. According to our prior published results, the continence rate at 3 mo was 55% overall, while it was 71% for grade 1 nerve-sparing group [19]. Our 1- (83%) and 3-mo (91%) continence rates were comparable with various

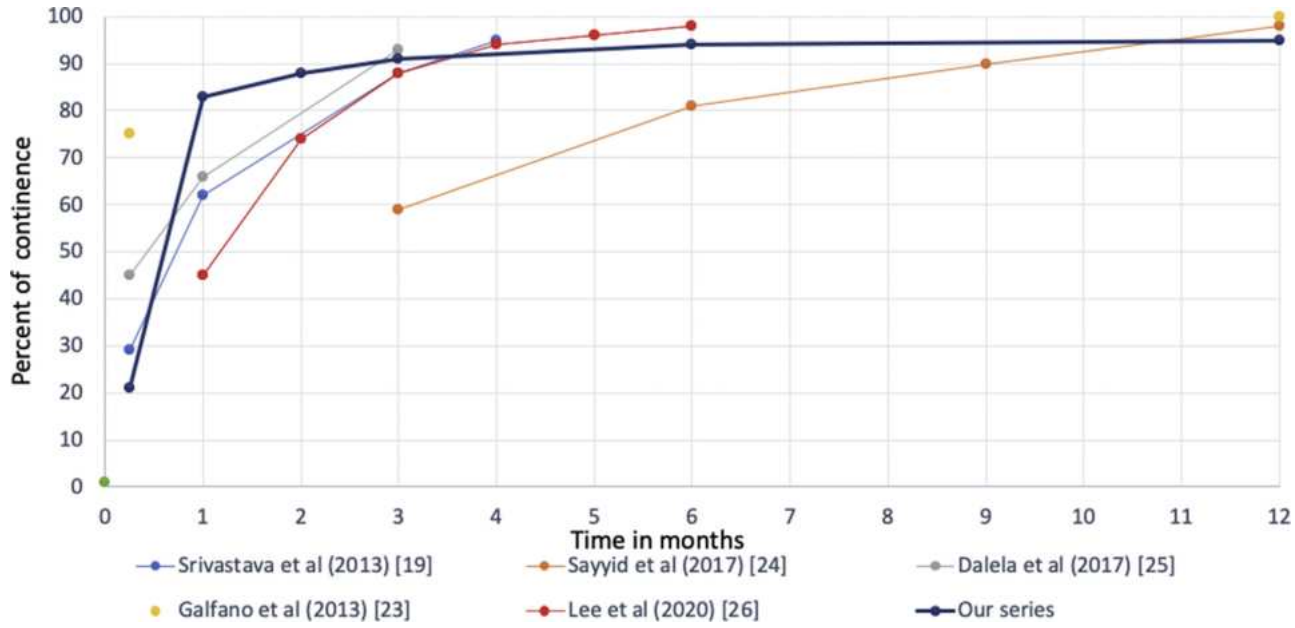

Fig. 5 – Continence rates of the hood technique, a previous study from the same group, and the published Retzius-sparing approach.

Table 5 – Comparison of pre-, intra-, and postoperative variables between the hood technique, previous study from the same group, and published Retzius-sparing approaches

Study authors	Srivastava et al [19]	Sayyid et al [24]	Dalela et al [25]	Galfano et al [23]	Lee et al [26]	Egan et al [32]	Our series
Study design	Case series Anterior (n = 1417)	Prosp Retzius (n = 100)	RCT Retzius (n = 60)	Prosp Retziu (n = 200)	Retro Retzius (n = 609)	Prosp Retzius (n = 70)	Prosp Anterior (n = 300)
Age (yr), median (IQR)	60 (55, 65)	61 (57, 66)	61 (55, 67)	65 (60, 69)	65 (60, 71)	62 ± 6[a]	64 (58, 68)
BMI (kg/m^2), median (IQR)	27 (25, 29)	29 (26, 32)	28 (26, 31)	26 (24, 28)	24 (22, 26)	28 ± 4[a]	27 (25, 29)
PSA (ng/mL), median (IQR)	4 (5, 7)	9 (6, 12)	6 (5, 7)	7 (5, 9)	14 ± 15[a]	4 ± 1[a]	6 (4, 8)
Biopsy Gleason Score (%)	GS 6: 47 GS 7: 43 GS ≥8: 10	GS 6: 19 GS 7: 62 GS ≥8: 19	GS 6: 30 GS 7: 70	GS 6:64 GS 7: 70 GS ≥8: 4	GS 6: 38 GS 7: 36 GS ≥8: 4	NA	GS 6 : 16 GS 7: 65 GS ≥8: 19
Clinical T stage (%)	T1: 72 T2: 27 T3: 1	≤cT2: 73 ≥cT3: 27	T1c: 67 T2ab:32 ≥T2c: 1	T1c: 65 T2a-b:27 T2c: 8	≤cT2: 49 ≥cT3: 51	T1: 71 T2: 19 T3: 10	T1: 51 T2: 35 T3: 14
Risk Category (%)	NA	D'Amico Low: 24 Int: 49 High: 27	NCCN Low: 23 Int: 77	D'Amico Low: 55 Int: 40 High: 5	NA	NA	CAPRA Low: 12 Int: 66 High: 22
IPSS (IQR)	7 (3, 12)	9 (5, 13)	7 (3, 12)	NA	13 ± 7[a]	NA	8 (4, 14)
IIEF/SHIM (IQR)	23 (15, 25)	NA	20 (14, 24)	NA	NA	NA	57 (35, 67)
Prostate size (g), median (IQR)	47 (38, 59)	45 (37, 56)	NA	NA	32 (26, 42)	NA	51 (40, 65)
Console time (min), median (IQR)	NA	120 (105, 142)	NA	120 (100, 150) 97 (80, 118)	149 ± 41[a]	130 ± 26[a]	118 (100, 140)
Blood loss (ml), median (IQR)	NA	100 (50, 200)	NA	300 (300, 500) 200 (200, 300)	280 ± 236[a]	100 (75–200)	150
Transfusion (%)	NA	0	0	0	3	NA	0
Catheter removal (d)	NA	10	NA	7	NA	NA	7

Table 5 (*Continued*)

Study authors	Srivastava et al [19]	Sayyid et al [24]	Dalela et al [25]	Galfano et al [23]	Lee et al [26]	Egan et al [32]	Our series
Complications Clavien-Dindo grade (%)	NA	NA	18	Grade I/II: 13 Grade III: 1–2	Grade III: 1	4.3	Grade I: 2.3 Grade II: 5.7 Grad III: 1.7
Pathologic stage (%)	pT2: 78 pT3: 22	pT2: 66 pT3: 34	NA	pT2: 68 pT3a: 34 pT3b: 4	pT2: 61 pT3: 39	pT2: 67 pT3a: 20 pT3b: 3	pT2: 81 pT3: 19
PSM T2 (%)	7.9	17	25	15	11	34.3	2.3
PSM T3 (%)		47	NA	45	36		3.7
Definition of continence	No Pads/24 hours	0–1 Pads/24 hours	No Pads/24 hours	No Pads/24 hours	≤1 safety liner/24 hours	No Pads/24 hours	No Pads/24 hours
Early continence	1 week: NA 1 month: NA 3 month: 56%	1 week: NA 1 month: NA 3 months: 59%	1 week: 45% 1 month: 66% 3 month: 93%	1 week: 75% 1 month: NA 3 month: NA	1 week: NA 1 month: 45% 3 month: 88%	1 week: NA 1 month: NA 12 month: 73%	1 week: 21% 1 month: 83% 3 month: 91%

BMI = Body mass index; IIEF: International index of erectile function; Int = Intermediate; IPSS: International prostate symptom score; IQR = Inter-quartile range; NA = Not available; PSM = Positive surgical margins; RCT = Randomized controlled trial; SHIM = Sexual health inventory for men questionnaire.
[a] Mean ± SD.

studies testing the Retzius-sparing approach, with rates of 45–66% and 59–93% reported, respectively (Fig. 5 and Table 5) [24–26]. The 1-yr continence rate with the hood approach was 95%, which is comparable with other anterior and posterior approaches.

Removal of the cancer is the most important outcome of RARP. Residual cancer after surgery can result in additional salvage therapies, with potential side effects for the patient and additional financial burden to an already strained healthcare system. The positive surgical margin rate achieved in this study using the hood technique was 6%, which includes final pathology as well as frozen section margins for all stages, while other studies using the Retzius-sparing technique report positive margin rates from 11% to 25% for pT2 cancers and from 36% to 47% for pT3 cancers (Table 5) [23–26]. The overall complication rate with the hood technique was 9.7%, well within the range of published rates of complications after RARP of 4.3–19.4% [27–31].

Finally, the hood approach enables visualization of common anatomical landmarks, which can be learned relatively quickly by most surgeons. The steps are reproducible and easy to learn. The ability to identify key landmarks (ie, median lobe, urethral orifices, endopelvic fascia, puboprostatic ligaments, external urethral sphincter, and the puboperinealis muscle) enables the surgeon to perform a safe oncological procedure with favorable continence outcomes. The hood technique allows the surgeon to tailor the dissection in the case of a visible anterior tumor and an enlarged prostate with a significant median lobe, which is often a concern with the Retzius-sparing approach. Hood technique's refinements to RARP result in the combined desirable outcomes of early continence and negative surgical margins, with minimal complications.

This study has several limitations: (1) it was conducted within a single health system by a single experienced surgeon, and therefore the results may not be reproducible by other surgeons; (2) it is a prospective study with no control arm, and the results of the study need to be verified in a randomized clinical trial; (3) we excluded cases with anterior tumor location, which may affect continence and oncological outcomes due to selection bias; and finally (4) the learning curve of Retzius-sparing approaches may reflect suboptimal outcomes in terms of margin rates and urinary continence outcomes.

5. Conclusions

Our novel hood technique represents modifications to the Retzius-sparing technique, which enables early return of continence without compromising surgical margin rates. Exclusion of anterior tumor location in the hood technique is quite reasonable and contributes to a reduction in the positive surgical margin rate while providing favorable functional outcomes. The hood technique and patient selection would be fit for current practice in the presurgical and prebiopsy MRI era.

Author contributions: Vinayak G. Wagaskar 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: Tewari, Wagaskar.
Acquisition of data: Wagaskar, Ratnani, Roy.
Analysis and interpretation of data: Wagaskar, Sobotka, Ratnani.
Drafting of the manuscript: Tewari, Wiklund, Wagaskar, Lewis, Mittal, Lantz, Falagario, Pathak, Dovey, Chakravarty, Nair, Martini, Haines.
Critical revision of the manuscript for important intellectual content: Wagaskar, Wiklund.
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Investigation. **Wagaskar, Ratnani, Sobotka:** Methodology. **Tewari, Wagaskar:** Project administration. **Pathak, Haines III, Martini, Dovey, Nair, Chakravarty:** Resources. **Wagaskar:** Software supervision. **Falagario, Treacy:** Validation. **Wagaskar, Mittal, Tewari, Wiklund, Lantz, Lewis:** Writing original draft. **Wagaskar, Wiklund, Tewari:** Writing-review and editing.

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.2020.09.044 and via www.europeanurology.com.

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Surgery in Motion

Urethral-sparing Robot-assisted Simple Prostatectomy: An Innovative Technique to Preserve Ejaculatory Function Overcoming the Limitation of the Standard Millin Approach

Francesco Porpiglia [a,*], *Enrico Checcucci* [a], *Daniele Amparore* [a], *Gabriel Niculescu* [a], *Gabriele Volpi* [a], *Federico Piramide* [a], *Sabrina De Cillis* [a], *Matteo Manfredi* [a], *Riccardo Autorino* [b], *Cristian Fiori* [a]

[a] *Department of Urology, "San Luigi Gonzaga" Hospital, University of Turin, Orbassano (Turin), Italy;* [b] *Division of Urology, VCU Health, Richmond, VA, USA*

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Abstract

Background: Despite recent technical innovations in the treatment of benign prostatic hyperplasia (BPH), retrograde ejaculation is still one of the most frequent adverse effects, with a major impact on patients' quality of life.
Objective: To evaluate the efficacy of our technique of urethral-sparing robotic-assisted simple prostatectomy (usRASP) in obtaining effective deobstruction and maintaining anterograde ejaculation, and secondarily, to compare these outcomes with those of a control group of patients who underwent standard robotic adenomectomy according to the Millin technique.
Design, setting, and participants: We prospectively enrolled patients between August 2017 and July 2019 with large BPH (prostate volume >80 ml) affected by significant BPH-related lower urinary tract symptoms (LUTS) who underwent usRASP. Then, a retrospective control group treated with standard Millin robotic-assisted simple prostatectomy (RASP) was selected.
Surgical procedure: The innovative aspect of our technique is the pivotal role of enucleation of the adenoma from all the anatomical structures, especially from the urethra. On the basis of the final results, the patients were divided into three groups (full, partial, or failed urethral sparing). Control group patients underwent standard Millin.
Measurements: All perioperative and follow-up data were collected, and descriptive, univariate, and multivariate analyses were performed.
Results and limitations: Ninety-two patients were enrolled. Full urethral-sparing adenomectomy was performed in 56 cases (60.86%). Urethral-sparing adenomectomy with minimal urethral infraction occurred in 21 cases (22.82%). In 15 patients (16.48%), the procedure was converted to standard RASP. Clavien grade ≥3 complications occurred in two patients (2%). Among the 70 patients with preoperative ejaculation, 57 (81%) maintained anterograde ejaculation at the 12th postoperative month. The maximum flow rate increased (17 m/s from baseline, $p = 0.034$), and International Prostate Symptom Score decreased rapidly (from 20 to 5 points; $p < 0.001$). With respect to the technique of the control group patients, usRASP allows the same perioperative and urinary functional outcomes, but with an improvement in terms of sexual function, especially for the ejaculation ($p < 0.001$ at every time point). A small sample size and short follow-up time are the major limitations of this study.
Conclusions: Urethral-sparing RASP has been found to be a safe and effective procedure that allows resolution of LUTS in large BPH and maintaining of ejaculatory function in a high percentage of patients.
Patient summary: Based on our findings, this technique should be considered as an option when counseling patients with large benign prostatic hyperplasia who are motivated to preserve antegrade ejaculation.

* Corresponding author. Division of Urology, Department of Oncology, School of Medicine, San Luigi Gonzaga Hospital, University of Turin, Regione Gonzole 10, 10043 Orbassano (Turin), Italy.
Tel.: +39 0119 026 558, Fax: +39 0119 038 654.
E-mail address: porpiglia@libero.it (F. Porpiglia).

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1. Introduction

Lower urinary tract symptoms (LUTS) are a growing problem in men over 50 yr of age [1]. They are often related to benign prostatic obstruction (BPO), and when prostate volume is >80–100 ml, simple prostatectomy (SP) might represent a valid alternative to transurethral techniques [2].

Open surgery is the gold standard approach for SP [3,4], but in recent years, minimally invasive techniques have been attempted worldwide, with interesting results [5].

In 2008, Sotelo et al [6] described, for the first time, robot-assisted simple prostatectomy (RASP). RASP appears to be attractive when compared with open SP, as RASP offers less blood loss and a shorter hospital stay [7].

Despite recent technical innovations, several postoperative problems are still unresolved. Among them, retrograde ejaculation is one of the most frequent problems, with a major impact on patients' quality of life [8,9].

To prevent this unwanted adverse event, the ejaculatory-sparing approach has gained popularity. Dixon et al [9] in 1990 described, for the first time, the urethral-sparing SP reporting maintenance of anterograde ejaculation. Quan et al [10] reported the same advantages, together with those of minimal invasiveness, performing the Madigan prostatectomy via a laparoscopic approach. Recently, Wang et al [11] described a first experiment with urethral-sparing RASP (usRASP).

We present our technique of usRASP, performed in a series of patients with large benign prostatic hyperplasia (BPH), even of the median lobe, in a high-volume robotic surgery center.

2. Patients and methods

2.1. Study design and aims

This is a prospective study enrolling, between August 2017 and July 2019, consecutive patients with voluminous BPH (prostate volume >80 ml) affected by significant hyperplasia-related LUTS, with indication for BPH surgery, who underwent RASP with urethral-sparing intent (usRASP).

The primary aim was to evaluate perioperative findings and functional outcomes (ejaculation and micturition) of the patients who underwent usRASP.

The secondary aim was to compare the results (in terms of micturition and sexual outcomes) of this population with those of patients treated with standard Millin robotic adenomectomy (standard RASP), whose data were extracted from our institutional database (control group).

2.2. Study population

2.2.1. Selection criteria and preoperative assessment for usRASP

All consecutive patients suitable for robotic adenomectomy during the study period were enrolled. This study was conducted in accordance with good clinical practice guidelines and was previously approved by an ethics committee; informed consent was obtained from the patients.

All patients were submitted to a preliminary examination, which included physical examination, prostate-specific antigen (PSA), and uroflowmetry. Patients with an indwelling catheter were excluded from the latter examination.

In case of elevated PSA, the patients underwent prostate multiparametric magnetic resonance imaging (mp-MRI), and subsequently a standard or target biopsy, to exclude the presence of prostate cancer. In case of PSA values in the range of 4–10 ng/ml and PSA density <0.15 ng/mL^2, MRI was not performed.

Moreover, to clearly assess prostate volume and postvoid urine residual (PVR), and to determine the potential presence and size of a median prostatic lobe protruding into the bladder, transrectal ultrasound was performed.

Finally, in order to define a baseline comparison, patients were given preoperative International Prostate Symptom Score (IPSS) [12,13] and International Index of Erectile Function (IIEF-5) questionnaires [14]. Moreover, specifically for the aim of our study, a dedicated evaluation of the ejaculation capability was performed using the short form of the internationally accepted Male Sexual Health Questionnaire to assess Ejaculation Dysfunction (MSHQ-EjD) [15].

2.2.2. Control group

Data on 92 patients who underwent standard RASP were extracted from our prospectively maintained database.

Demographics and preoperative variables of the two cohorts were compared in terms of age, body mass index, prostate volume, presence of a median lobe, and IIEF-5, to verify the comparability of the patients.

2.2.3. Follow-up

Follow-up visits were performed at 1, 3, 6, and 12 mo postoperatively.

Postoperative assessment included physical examination and evaluation of PVR, uroflowmetry with maximum flow rate (Qmax), PSA, IPSS, quality of life (QoL), IIEF-5, and MSHQ-EjD.

Patients whose urethra was spared underwent flexible cystoscopy in an ambulatory setting in order to evaluate the aspect of the prostatic urethra at the 3rd month after intervention.

Specifically for this study, after obtaining dedicated consent, for patients who underwent preoperative prostate mp-MRI at 6 mo postoperatively, prostate mp-MRI was repeated in case of persistently high PSA or incidental prostate cancer findings.

Moreover, at the same time point, patients who still maintained ejaculation after the intervention and were judged to have effective ejaculation were recommended a spermiogram, to prove the presence of spermatozoa in the seminal fluid.

2.3. Surgical technique

All adenomectomies were performed by a single, highly experienced, surgeon using a da Vinci Si or XI Surgical System (Intuitive Surgical, Sunnyvale, CA, USA).

2.3.1. Urethral-sparing RASP

2.3.1.1. Patient position, port placement, and docking of the robotic system. Under general anesthesia, the patient is prepared and positioned in a slight (27°) Trendelenburg position. Pneumoperitoneum is achieved using a Veress needle inserted in the periumbilical area.

Six ports (12 mm port for the optic for SI or 8 mm for XI, three 8 mm ports for robotic instruments, and 10 and 5 mm ports for the assistant) are placed in a classical fan configuration. Finally, the robot is docked.

2.3.1.2. Preliminary time and preparation of the cleavage plane. After the parietal peritoneum is incised to gain access to the retropubic space and prostate defatting is performed, a transversal anterolateral incision is made halfway between the dorsal venous complex and the bladder neck (Fig. 1A). The cleavage plane between the surgical capsule and the adenoma is identified anteriorly, and gently dissected at the prostate apex bilaterally (Fig. 1B).

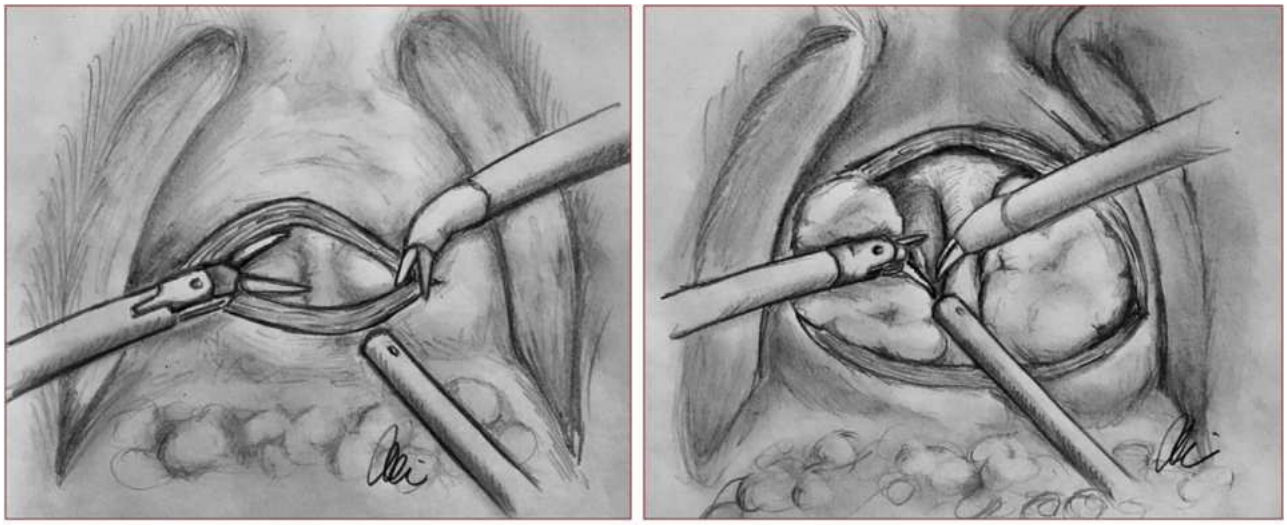

Fig. 1 – (A) A transversal anterolateral incision is made halfway between the dorsal venous complex and the bladder neck, done according to Millin. (B) The median face of the adenoma was dissected gently form the urethra.

2.3.1.3. Dissection of the adenoma. Adenoma enucleation is performed following the avascular plane of the surgical capsule, starting from the left lobe. The dissection proceeds anteriorly from the prostate's apex bilaterally to the left lateral face of the adenoma, then cranially at the bladder neck. Bipolar forceps are used to control possible bleeding from perforating blood vessels.

It is useful to emphasize that, in order to avoid straying into the capsular plane, the entire dissection must tightly adhere to the adenoma's surface.

At the end of this step, the left lobe is mobilized, except for its medial portion, which is still anchored to the urethra. Subsequently, a median longitudinal incision is made at the anterior commissure. The urethra is medialized by the assistance of a suction device and gently dissected from the left lobe of the adenoma.

Often, especially in cases of large adenomas, the left lobe is in continuity with the right lobe, posteriorly to the urethra. In these cases, an incision of the adenoma is needed, and if the posterior tissue is abundant, it can be removed separately.

Finally, the posterior aspect of the surgical capsule is reached with a caudocranial dissection. The left lobe is then removed.

The procedure is repeated for the right lobe.

After the removal of the adenoma (Fig. 2A and 2B), a hydrodistension test is performed, filling the bladder with 150 ml of saline solution, in order to verify urethral and bladder integrity.

Any perforation is sutured with a 4-0 absorbable monofilament. Any bleeding is controlled; eventually, a thrombin gelatin hemostatic matrix is injected at the prostatic lodge to facilitate hemostasis. Finally, the prostatic capsule is closed with a running two-layer 3/0 barbed suture.

In the presence of a median lobe, after the two lateral lobes are removed, a 2 cm median longitudinal incision is made at the anterior face of the bladder, previously filled with 150 ml of saline solution. A transversal incision at the mucosa covering the median lobe is

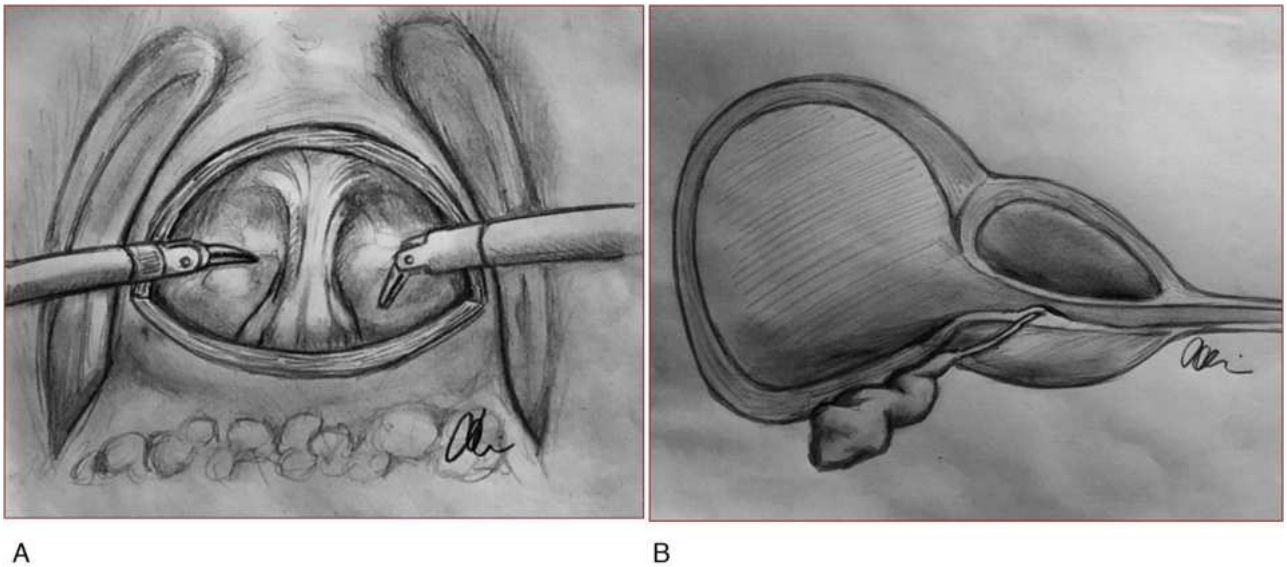

Fig. 2 – (A) At the end of the extirpative phase, the adenoma was removed and the urethra was spared inside the prostatic lodge. (B) As shown, the urethra and ejaculatory ducts were preserved.

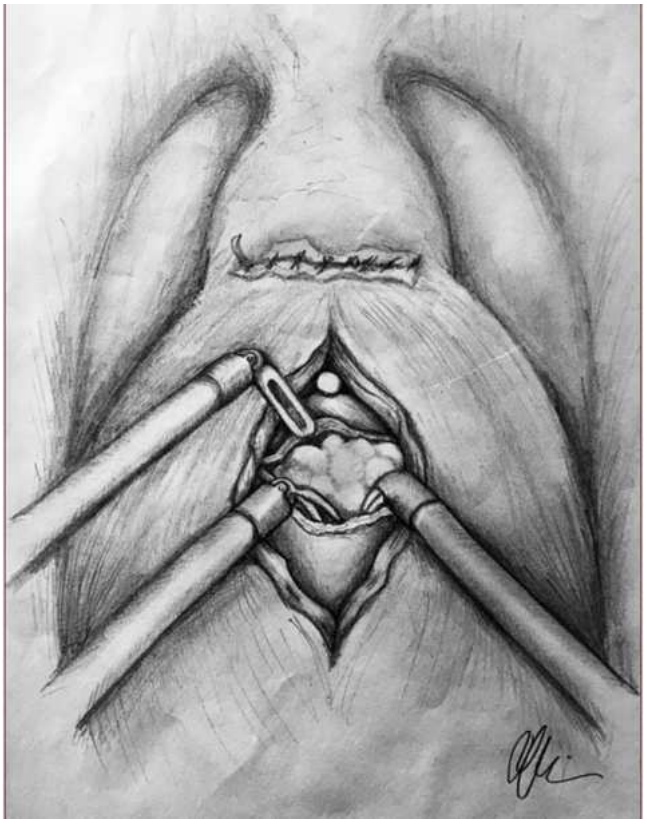

Fig. 3 – In case of a median lobe not manageable with transcapsular approach, an incision of the bladder wall is needed in order to reach it. A transversal incision at the level of mucosa covering the median lobe is then performed, and the third lobe is exposed with an upward traction from behind the bladder neck. With this traction, it is progressively dissected.

performed (Fig. 3). The third lobe is then exposed, and using upward traction from behind the bladder neck, it is progressively dissected and then resected. Then, the previously incised mucosa is sutured with a barbed running suture.

During this phase, there is the risk of detaching the urethra from the median lobe, which can be damaged, particularly in its cranial portion.

If this occurs, the urethral-sparing approach is not applicable, and then the whole urethra has to be removed and "trigonization" performed.

Finally, the bladder wall is sutured with a two-layer 3/0 barbed running suture.

2.3.2. Control group

In all patients of the control group, a standard RASP according to the Millin technique was performed, namely, no urethral-sparing technique was used and "trigonization" was performed.

2.4. Postoperative care

A 20 F three-way catheter is placed before the prostatic capsule closure and left in place. After the procedure, continuous bladder irrigation (CBI) was maintained for 24 h. If significant hematuria persists, CBI is prolonged. Antibiotic prophylaxis with cephalosporin is administered from the day of intervention to the day of discharge. We recommend ambulation from the 2nd postoperative day (POD).

The extraperitoneal drainage is removed on the 2nd POD. The catheter is routinely removed during the 3rd and 5th POD, depending on the degree of hematuria. We opted to maintain the catheter up to the 3rd–5th POD, in order to reduce the risk of urinary retention due to the presence of urethral mucosal edema.

2.5. Data collection

The prospectively maintained database included the following patient characteristics: age, body mass index, baseline symptoms, American Society of Anesthesiologists score, prostate volume on transrectal ultrasound, pre- and postoperative PSA, PVR, uroflowmetry, IPSS, and IIEF-5 score. The patients were defined as "potent" with an IIEF-5 score of >17 [14]. An additional MSHQ-EjD scale questionnaire concerning ejaculation was submitted to patients with no postoperative erectile dysfunction.

Perioperatively collected data included estimated blood loss, operative time, catheterization duration, length of stay, and postoperative complications.

For the purpose of this study, patients who underwent usRASP were classified into three different groups:

1 Full urethra preservation (when the urethra was completely spared).
2 Minimal urethra injury (when a minimal laceration of the urethra occurred, and subsequently a dedicated suture was needed).
3 No preservation of the urethra (when preservation of the urethra was not possible, and a standard Millin adenomectomy was performed).

Postoperative complications were classified according to Clavien et al [16]. Pathological data included specimen weight and histological diagnosis.

The same data (with the exception of the data on urethral preservation) were extracted for the control group.

2.6. Statistical analysis

Continuous variables are summarized as median and interquartile range (IQR). Categorical variables are reported as frequencies (%). If data followed the normal distribution, a t test was used; otherwise, a nonparametric test was used (Mann-Whitney U test). A two-sided value of $p < 0.05$ is considered statistically significant. The Mann-Whitney U test assessed any difference between patients who maintained ejaculation and those who did not.

A univariable analysis between the primary outcome (preservation of ejaculation) and other variables was performed. Based on the variables found to be significant at the univariable analysis, a multivariable logistic regression model for the preservation of ejaculation was built. Data analysis was performed using StatSoft version 10.

3. Results

3.1. Demographics and preoperative variables

Ninety-two patients were enrolled in our study. Among them, 22 (23.4%) had an indwelling catheter and 83 (90.0%) used alpha-blockers.

The median age was 67 (IQR 64.3–70.8) yr. The median prostate volume was 140 (IQR 119–171) ml, and 34 (36.0%) patients had a median lobe. At baseline, the median IPSS, QoL, and IIEF-5 scores were 20 (IQR 16–24.8), 5 (IQR 4–6), and 18 (IQR 12–20), respectively. Seventy-five (81.5%)

Table 1 – Patient demographics and characteristics.

Patient demographics	usRASP (92 pts)	Control group (92 pts)	*p* value
Age (yr) median (IQR)	67 (64.3–70.8)	68 (64–71)	0.3
BMI (kg/m^2), median (IQR)	26.7 (25–30)	26.4 (24.3–29)	0.5
Age-adjusted Charlson comorbidity index, median (IQR)	3 (2–6)	3 (2–6)	1
IPSS, median (IQR)	20 (16–24.8)	21 (17–27)	0.4
QoL, median (IQR)	5 (4–6)	5 (4–6)	1.00
IIEF-5, median (IQR)	18 (12–20)	19 (11–19)	0.4
Prostate volume (ml), median (IQR)	140 (119–171)	135 (108–170)	0.5
PSA (ng/mL), median (IQR)	9.7 (6.00–16.6)	9.8 (5.75–15.96)	0.9
PVR (ml), median (IQR)	150 (57.5–163)	150 (80–180)	1.00
Qmax (ml/s), median (IQR)	8 (6.25–11)	9 (6.80–10.80)	0.1
Median lobes, *n* (%)	34 (37)	37 (40.2)	0.8
Median lobe length (cm), median (IQR)	1.4 (1.00–1.78)	1.6 (1.10–1.93)	0.8
BPH-related complications, *n* (%)	53 (58)	58 (63)	0.6
Urinary retention/indwelling catheter	22 (24)	25 (27.1)	0.8
Bladder stone	7 (8)	6 (6.5)	0.9
Recurrent urinary tract infection	11 (12)	13 (14)	0.8
Recurrent hematuria	13 (14)	13 (14)	0.8
Hydronephrosis	0	0	NA
Bladder diverticulum	0	1 (1.08)	0.9

BMI = body mass index; BPH = benign prostatic hyperplasia; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; NA = not available; PSA = prostate-specific antigen; pts = patients; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; usRASP = urethral-sparing robot-assisted simple prostatectomy.

patients had valid sexual activity (IIEF-5 score ≥17) before the intervention or the date of catheterization. Among them, 70 (76.0 %) had normal ejaculation preoperatively or before the beginning of alpha-blocker therapy. The median MSHQ-EjD short form (MSHQ-EjD-SF) score was 9 (IQR 6–11) preoperatively.

All preoperative baseline characteristics are summarized in Table 1.

3.2. *Perioperative findings*

The intraoperative findings revealed that the following:

1 Full ureteral-sparing adenomectomy was performed in 56 cases (60.86%).
2 Urethral-sparing adenomectomy with minimal urethral infraction that required dedicated suture with 4/0 monofilament stich was performed in 21 cases (22.82%).
3 Failed urethral-sparing adenomectomy, converted to standard RASP, occurred in 15 cases (16.48%); in four of these cases, it occurred during the removal of the third lobe.

None of the procedures were converted into open or pure laparoscopic SP.

The median operative time was 110 (IQR 97–122) min; median estimated blood loss was 200 (IQR 190) ml. No intraoperative complications were registered (Table 2). The median specimen weight of the resected adenoma was 90 (IQR 75–117) g.

Table 2 – Intraoperative variables and postoperative complications reported according to Clavien-Dindo classification.

	usRASP (92 pts)	Control group (92 pts)	*p* value
Intraoperative time (min), mean (SD)	110 (97–122)	105 (100–120)	0.1
Estimated blood loss, median (IQR)	200 (110–300)	175 (190)	0.4
Hospital stay, median (IQR)	5 (4–6)	5 (4–6)	1.0
Catheterization time, median (IQR)	4 (3–6)	5 (4–6)	0.1
Intraoperative complications, *n* (%)	0 (0)	2 (2)	0.5
Postoperative complications, *n* patients (%)	13 (14)	14 (15)	0.9
Grade 1	0 (0)	0 (0)	NA
Grade 2			
Mild hematuria after catheter removal	3 (3)	2 (2)	1.0
Acute urinary retention after catheter removal	2 (2)	3 (3)	1.0
Fever, desaturation, delirium, syncope	4 (4)	5 (5)	1.0
Urine leakage	2 (2)	2 (2)	0.6
Grade 3a	0 (0)	0 (0)	NA
Grade 3b			
Acute urinary retention after catheter removal due to intravesical clots requiring endoscopic removal	1 (1)	0 (0)	0.9
Pelvic hematoma requiring surgical drainage	1 (1)	2 (2)	1.0
Grade 4 or 5	0 (0)	0 (0)	NA

IQR = interquartile range; NA = not available; SD = standard deviation; usRASP = urethral-sparing robot-assisted simple prostatectomy.

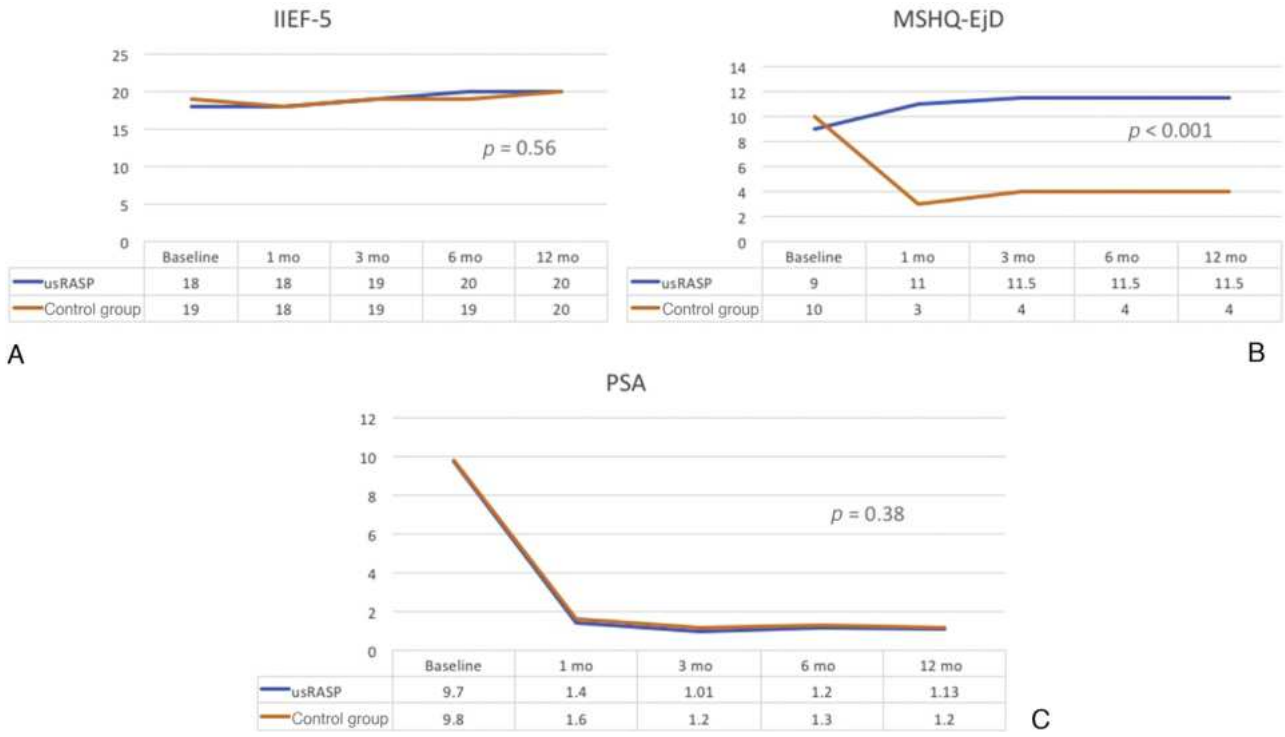

Fig. 4 – Erection and ejaculation outcomes were reported at baseline and during the follow-up period in terms of (A) IIEF-5 and (B) MSHQ-EjD-SF. (C) PSA values were followed during the study period.
IIEF-5 = International Index of Erectile Function; MSHQ-EjD-SF = Male Sexual Health Questionnaire Ejaculation Dysfunction—short form; PSA = prostate-specific antigen; usRASP = urethral-sparing robotic-assisted simple prostatectomy.

An analysis confirmed BPH + chronic prostatitis in 80 (87.0%) patients, with only eight (8.7%) cases of prostatic adenocarcinoma (six had pT1a Gleason score [GS] 3 + 3, one had pT1b GS 3 + 3, and one had pT1b GS 3 + 4) and four (4.3%) cases of high-grade prostatic intraepithelial neoplasia.

The median hospital stay was 5 (IQR 4–6) d, and the median catheterization time was 4 (IQR 3–6) d.

Postoperative complications are reported in Table 2:

1 Complications defined as ≥3 grade according to Clavien-Dindo classification occurred in only two patients (2%): one with retropubic hematoma requiring surgical evacuation and the other with acute urinary retention due to intravesical clots requiring endoscopic removal.
2 Complications of <3 grade of the Clavien-Dindo scale were reported in 11 cases (12%). Urine leakage as well as acute urinary retention occurred in two patients. Both conditions were resolved by re-placing a 20 F Foley catheter that was left in place for 5 d.

3.3. *Ejaculation outcomes*

The mean follow-up duration was 12 mo, and all patients had a minimum follow-up period of 9 mo. Focusing on sexual outcomes, potency was not significantly influenced by the intervention, and no differences were found between pre- and postoperative values of IIEF-5 scores ($p > 0.05$; Fig. 4A).

Among the 70 patients who had ejaculation before the intervention, 44 (63%), 56 (80%), 57 (81%), and 57 (81%) maintained anterograde ejaculation, respectively, at 1, 3, 6, and 12 mo postoperatively.

The median time to recovery was 3 (standard deviation [SD]: 2.5) mo postoperatively, without differences in case of the median lobe.

Of these patients, the urethra was completely spared or minimally infracted in 59 cases (84.3%), with recovery or maintenance of anterograde ejaculation 3 and 12 mo after surgery in 85% and 89% of these cases, respectively.

The patients showed a progressive increase in spermatic volume from the 1 st to the 6th month of follow-up. No differences were found if a minimal urethra laceration occurred or the urethra was completely spared at any time point ($p > 0.5$).

Among the 57 patients with valid ejaculation at 6th month postoperatively, the spermiogram collected revealed a mean volume of seminal fluid of 3 (SD: 2.6) ml, with a mean number of spermatozoa per milliliter of 14 (SD: 3.6) million.

From the MSHQ-EjD-SF questionnaire, an improvement from the baseline value of 9 points at 1 and 3 mo of follow-up was recorded ($p < 0.05$). Then the value remained stable until the 12th month after surgery (Fig. 4B and 4C and Tables 3 and 4).

Table 3 – Pre- and postoperative functional outcomes and PSA values during the follow-up period.

	usRASP (92 pts)	Control group (92 pts)	*p* value
IPSS, median (IQR)			
Preoperative	20 (16–24.8)	21 (17–24)	0.4
1 mo	5 (3–10)	6 (4–11)	0.3
3 mo	5 (3–8)	5 (3–8)	1.0
6 mo	5 (3.5–6)	5 (3.5–6)	1.0
≥12 mo	5 (4.25–6)	5 (4.25–6)	1.0
QoL, median (IQR)			
Preoperative	5 (4–6)	5 (4–6)	1.0
1 mo	1 (0–2)	1 (0–2)	1.0
3 mo	1 (0–2)	1 (0–2)	1.0
6 mo	1 (0–2)	1 (0–2)	1.0
≥12 mo	1 (0–2)	1 (0–2)	1.0
IIEF-5, median (IQR)			
Preoperative	18 (12.3–20)	19 (10–22)	0.4
1 mo	18 (10–21)	18 (10–21)	1.0
3 mo	19 (10–22)	19 (10–21)	1.0
6 mo	20 (11–22)	19 (10–21)	0.5
≥12 mo	20 (10–22)	20 (12–22)	1.0
MSHQ-EjD, median (IQR)			
Preoperative	9 (6–11)	10 (5–11)	0.2
1 mo	11 (7–12)	3 (2–5)	<0.001
3 mo	11 (8–12)	4 (2–5)	<0.001
6 mo	11 (8–12)	4 (2–5)	<0.001
≥12 mo	11 (8–12)	4 (2–5)	<0.001
Incontinence, *n* (%)			
Preoperative	0 (0)	0 (0)	NA
1 mo	0 (0)	2 (2)	0.5
3 mo	0 (0)	0 (0)	NA
6 mo	0 (0)	0 (0)	NA
≥12 mo	0 (0)	0 (0)	NA
Ejaculation preservation, *n* (%)			
Preoperative	70/92 (75)	68/92 (73.9)	1.0
1 mo	44/70 (63)	5/68 (7.3)	<**0.001**
3 mo	56/70 (80)	6/68 (8.8)	<**0.001**
6 mo	57/70 (81)	6/68 (8.8)	<**0.001**
≥12 mo	57/70 (81)	6/68 (8.8)	<**0.001**
Qmax (ml/s), median (IQR)			
Preoperative	8 (6.25–11)	9 (6–11)	0.1
1 mo	25 (20.5–29.8)	23 (20.5–28)	0.1
3 mo	25 (20–29)	24 (20.8–30)	0.4
6 mo	24 (20–30.5)	24 (20–30.5)	1.00
≥12 mo	24 (20–29)	25 (20–29)	0.4
PVR (ml), median (IQR)			
Preoperative	150 (57.5–163)	150 (80–180)	1.00
1 mo	76 (46–110)	62 (38–120)	0.3
3 mo	63 (23–88)	54 (20–94)	0.4
6 mo	35 (20–66)	36 (20–58)	0.9
≥12 mo	18 (10–36)	15 (12–33)	0.4
PSA (ng/mL), median (IQR)			
Preoperative	9.70 (6.00–16.6)	9.8 (6.67–16.29)	0.9
1 mo	1.57 (0.97–2.45)	1.6 (0.58–1.80)	0.3
3 mo	1.03 (0.65–1.39)	1.2 (0.55–1.78)	0.1
6 mo	1.20 (0.91–1.76)	1.3 (0.65–1.90)	0.4
≥12 mo	1.20 (0.47–1.49)	1.2 (0.30–1.77)	0.6

IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; MSHQ-EjD = Male Sexual Health Questionnaire Ejaculatory Dysfunction (range 0–15); NA = not available; PSA = prostate-specific antigen; pts = patients; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life; usRASP = urethral-sparing robot-assisted simple prostatectomy.

3.3.1. *Univariate and multivariate analysis*

As observed from the univariate analysis, age at surgery, adenoma volume, median lobe, and the absence of urethral infraction were predictors of maintenance of ejaculation.

The multivariable logistic regression model showed that younger age at surgery (odds ratio [OR] 0.87, $p = 0.012$) and absence of urethral infraction (OR 0.87, $p = 0.022$) were the only predictors of ejaculation recovery at the 3rd postoperative month (Supplementary Table 1).

Ejaculation recovery at the 12th month was influenced only by age at surgery (OR 0.90, $p = 0.010$; Supplementary Table 2).

Table 4 – Micturition and sexual outcomes during the follow-up period of the patients who underwent urethral-sparing adenomectomy.

Follow-up time point	IPSS, median (IQR)	QoL, median (IQR)	IIEF-5, median (IQR)	MSHQ-EjD, median (IQR)	Incontinence, *n* (%)	Ejaculation preservation (%)	Qmax (ml/s), median (IQR)	PVR (ml), median (IQR)
Preoperative (92 pts)	20 (16–24.8)	5 (4–6)	18 (12.3–20)	9 (6–11)	0 (0)	70/92 (75)	8 (6.25–11)	150 (57.5–163)
Postoperative								
1 mo	5 (3–10)	1 (0–2)	18 (10–21)	11 (7–12)	0 (0)	44/70 (63)	25 (20.5–29.8)	76 (46–110)
3 mo	5 (3–8)	1 (0–2)	19 (10–22)	11 (8–12)	0 (0)	56/70 (80)	25 (20–29)	63 (23–88)
6 mo	5 (3.5–6)	1 (0–2)	20 (11–22)	11 (8–12)	0 (0)	57/70 (81)	24 (20–30.5)	35 (20–66)
≥12 mo	5 (4.25–6)	1 (0–2)	20 (10–22)	11 (8–12)	0 (0)	57/70 (81)	24 (20–29)	18 (10–36)
p value	<0.001	0.012	0.08	0.1	–	0.3	0.034	0.045

IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; MSHQ-EjD = Male Sexual Health Questionnaire Ejaculatory Dysfunction (range 0–15); pts = patients; PVR = postvoid residual; Qmax = maximum flow rate; QoL = quality of life.

3.4. *Micturition outcomes*

Concerning urinary functional outcomes, Qmax was 8 (IQR 6.25–11) ml/s at baseline, with a PVR of 150 (IQR 57.5–163) ml; the median IPSS was 20 (IQR 16–24.8) and QoL score was 5 (IQR 4–6).

The median Qmax at a 3-mo follow-up visit was 25 (IQR 20.5–29.8) ml/s, with an increase of 17 ml/s from baseline ($p < 0.05$; +212%). During the subsequent follow-up period, only a slight decrement was recorded, with the median Qmax being 24 (IQR 20–29) ml/s at 12 mo from the intervention.

PVR decreased gradually over time.

IPSS rapidly decreased 1 mo postoperatively (from 20 to 5 points, $p < 0.05$). Then, the score was recorded to be stabilizing substantially during the follow-up period (IPSS: 5, IQR 2.25 at 1 yr of follow-up).

In parallel, patients reported enhanced QoL, made evident by a median score of 1 (±3) registered at the 1-mo follow-up visit, and further improving until reaching 1 (±2) at 12 mo from surgery. The Mann-Whitney *U* test found a statistically significant difference between the pre- and postoperative IPSS and Qmax at each follow-up time ($p < 0.001$; Fig. 5).

No patients were found to be incontinent at any time point (Table 3).

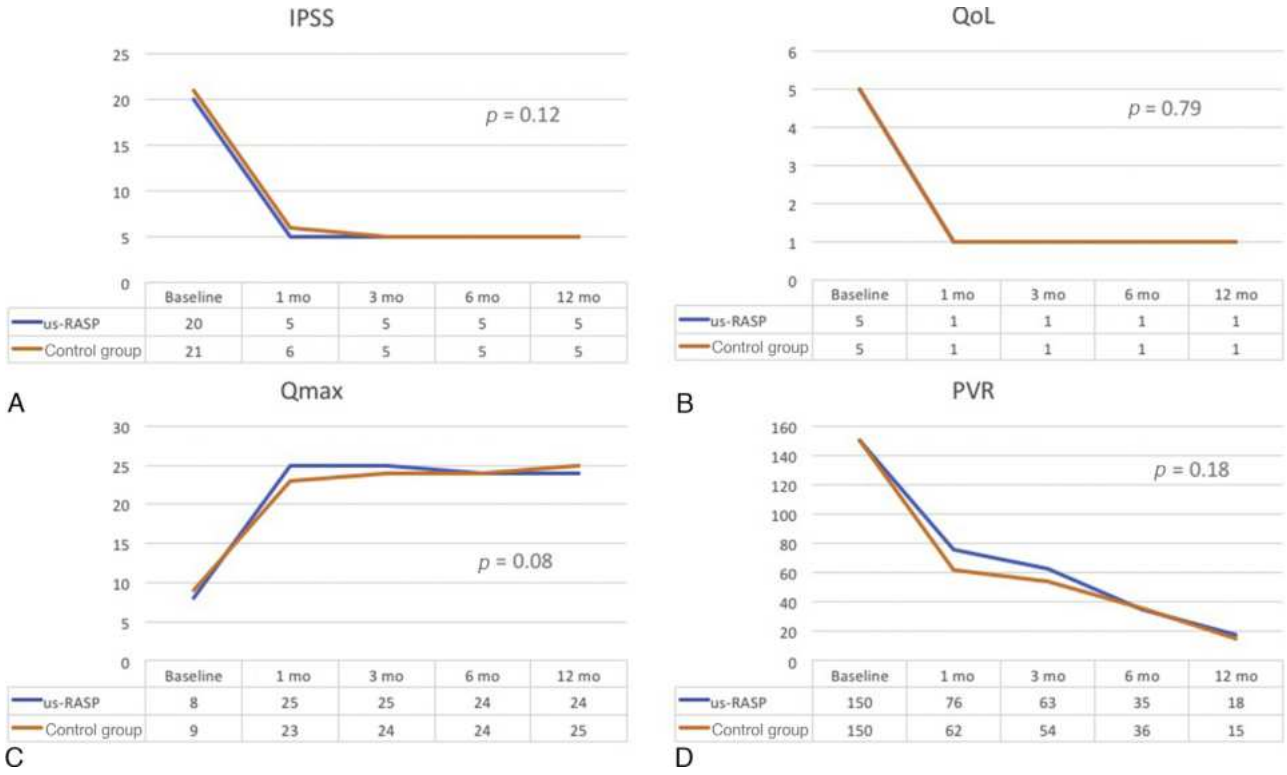

Fig. 5 – Micturition functional outcomes were reported at the baseline and during the follow-up period in terms of (A) IPSS, (B) QoL, (C) Qmax, and (D) PVR.
IPSS = International Prostate Symptom Score; PVR = postvoid urine residual; Qmax = maximum flow rate; QoL = quality of life; usRASP = urethral-sparing robotic-assisted simple prostatectomy.

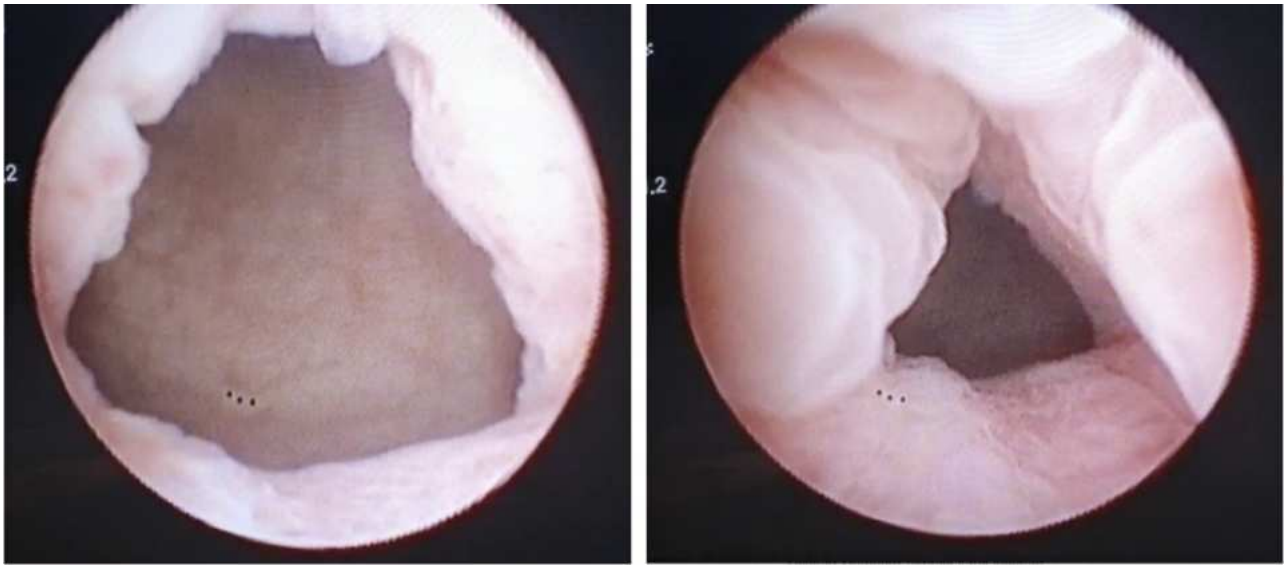

Fig. 6 – The 3rd month postoperative cystoscopy of a patient who underwent usRASP, showing that the bladder neck and urethra were deobstructed, even if slight edema was still observed. This patient was 65 yr old; prostate volume was 120 cc, with a 1.5 cm median lobe; operative time was 95 min; and no intra- or postoperative complications occurred.
usRASP = urethral-sparing robotic-assisted simple prostatectomy.

At 3 mo after the intervention, in patients in whom the urethra was spared, flexible cystoscopy did not show urethral stenosis or necrosis (Fig. 6). Moreover, cystoscopy revealed the integrity of the mucosa of prostatic urethra, without extrinsic compression deforming its walls. The median lobe was found to be completely removed.

Preoperatively, 22 (23.9%) patients underwent prostate mp-MRI due to elevated PSA (Fig. 7A). Among them, 10 patients repeated the mp-MRI at the 6th month of follow-up, showing complete removal of the adenoma, and integrity of the urethra and prostate capsule (Fig. 7B). In particular, re-expansion of the prostatic capsule was observed, and a near space was observed between the urethra and the capsule. No suspicious areas for prostate cancer were recorded.

3.5. *Urethral-sparing RASP versus control group*

The last 92 patients who underwent standard Millin robotic adenomectomy were retrospectively extracted from our

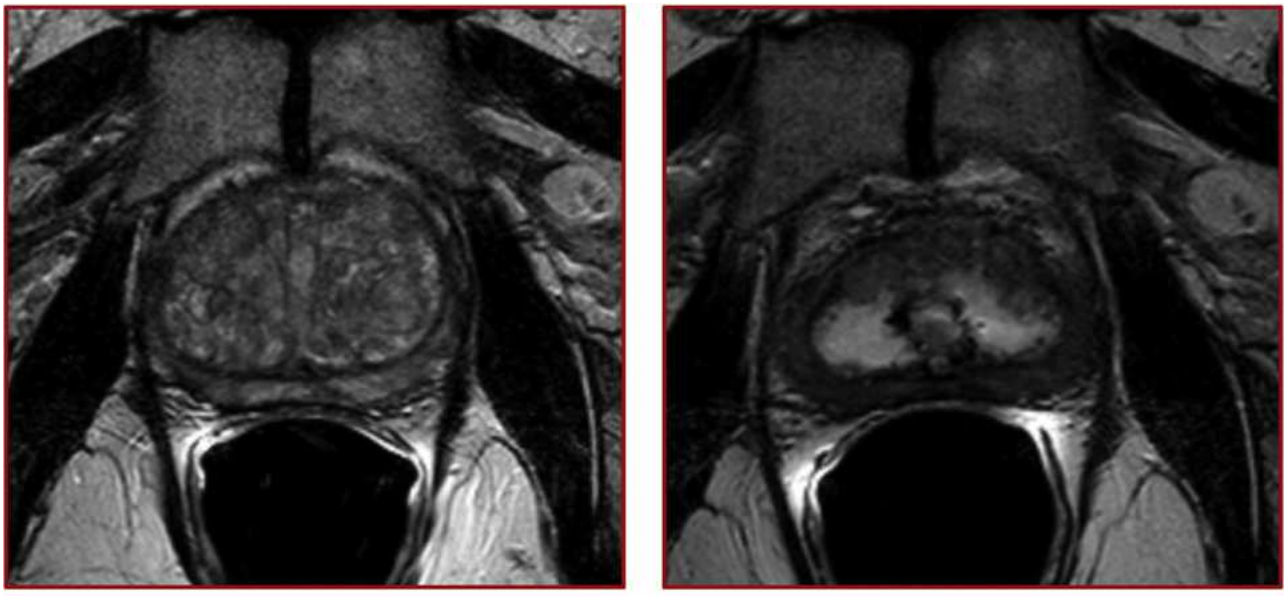

Fig. 7 – (A) Preoperative mp-MRI showed a large and obstructive prostatic adenoma. (B) The 6th month postoperative mp-MRI showed a wide prostatic lodge. This patient was 67 yr old; prostate volume was 110 cc, with a 1.8 cm median lobe; operative time was 100 min, and no intra- or postoperative complications occurred.
mp-MRI = multiparametric magnetic resonance imaging.

database. No differences were found between the characteristics of patients and adenomas between the two groups (Table 1).

Moreover, no differences were found intraoperatively or in postoperative complications (Table 2).

Concerning the micturition outcomes, the two techniques were found to be comparable in terms of IPSS, QoL, Qmax, PVR, and continence rate at every time point (Table 3).

The ejaculation preservation rate was found to be significantly higher for usRASP during the entire follow-up period ($p < 0.001$ at every time point).

Similarly, the MSHQ-EjD questionnaire was shown to reach better scores when the urethra was preserved ($p < 0.001$ at every time point; Table 3).

4. Discussion

For many years, urologists have thought that retrograde ejaculation or dry orgasm or both were unavoidable consequences of BPH-related surgical procedures [17]. However, these side effects are associated with lower quality of life, reduced self-confidence, and relationship issues [18] related not only to orgasmic function, but also to fertility. This is a growing problem due to the early onset of BPH and the increase in life expectancy [19].

In order to solve this matter, surgeons and physiopathologists have studied in more detail male anatomy and ejaculatory function [20].

Contrary to what was considered true for a very long time, bladder neck closure is not essential for antegrade ejaculation, as demonstrated during transurethral incision of the prostate (TUIP) [21,22]. Gil-Vernet et al [20] studied ejaculation by recording endorectal ultrasound videos during masturbation in 30 men and demonstrated a crucial function of muscular tissue during ejaculation: the verumontanum makes contact with the opposite side of the urethra wall, and the sperm emitted in the urethra from the ejaculatory ducts is conducted distally by the contractions of the external sphincter and the bulbar urethra. This area was defined as "high-pressure ejaculatory area." This study raises speculation that if tissues around the verumontanum are not injured, ejaculation should occur even with an open bladder neck [23].

Subsequently, surgeons have tried to modify surgical procedures in order to preserve ejaculation [24], even for endoscopy; and the holmium laser enucleation of the prostate seems to be the gold standard treatment, especially for large prostate [25,26].

Recently, Cacciamani et al [17], in their systematic review and pooled analysis, showed that patients undergoing endoscopic procedures using Greenlight, prostate artery embolization, or thulium laser enucleation of the prostate had a lower, but not statistically significant, relative risk of retrograde ejaculation than those undergoing conventional transurethral resection of the prostate (TURP; relative risk [RR]: 0.90, $p = 0.35$; RR: 0.71, $p = 0.1$; RR: 0.73, $p = 0.11$). These techniques were revealed to have the same efficacy as TURP. In the analysis, it emerged that new technological alternatives might improve sexual outcomes, especially for nonablative treatments. Among them, the Aquablation technique revealed stability in MSHQ-EjD questionnaire results after the intervention, with a statistically significant lower rate of anejaculation than TURP [27]. It could be due to the possibility of preserving the verumontanum with accurate treatment planning. Moreover, the Rezum system, a water-vapor delivery device that is inserted into the transition zone of the prostate under direct visualization, allowed preservation of ejaculation up to 36 mo of follow-up [24].

Regarding open surgery, in 1974, Dixon et al [9] published the first experiments employing their new "Madigan prostatectomy technique." The novelty of this surgical technique was preservation of urethra integrity, in order to reduce potential postoperative issues. As for sexual function, the 24 patients who were potent at baseline showed normal ejaculation after the intervention. Orgasm quality and sexual satisfaction were not modified.

In the following years, different modified Madigan SP techniques were proposed, even with a laparoscopic approach [10,28].

However, Madigan prostatectomy has not become widely used, mainly because of the technical complexity of the preservation of the prostatic urethra. Today, in the era of robot-assisted surgery that allows for better visualization, dissection, and suturing, a wider use of urethral-sparing techniques has been proposed.

Wang et al [11] and Simone et al [29] have recently conceived a new technique of urethral-sparing robot-assisted prostatectomy. The main limitations of these studies are the small sample size (27 and 10 patients, respectively), short follow-up, exclusion of patients with a median lobe, and many surgical details that were consequently not reported.

In this paper, with the aim to analyze all technical details of urethral-sparing adenomectomy, even in case of a median lobe, we present the final technical refinement of our technique and functional results after 1 yr of follow-up.

Of our 92 enrolled patients, 77 (83.7%) showed a urethral preservation. Only in 15 cases (16.48%), urethral preservation was not possible.

The failure in preservation can be due to (1) a urethral wall that is very thin due to a loss of muscular fiber architectural structures, (2) the posterior development of the adenoma behind the posterior urethral wall, or (3) the presence of a median lobe strictly adhering to the posterior wall of the cranial urethra.

Focusing on patients with a median lobe, excluded in previously published series, transcapsular access is not a possible approach, so a longitudinal bladder incision is needed in order to remove it.

Among the 34 patients with a median lobe, urethral laceration occurred only in four patients (11.7%).

A statistically significant reduction of IPSS (from 20 to 5 points) with an improvement of QoL score (from 5 points to 1 point) at 1 yr of follow-up was observed. The quality of the resolution of BPO by the urethral-sparing technique was

found to be comparable with the standard Millin approach, as outlined by the similar micturition outcomes found in such a cohort of patients (Table 3).

Moreover, among the 70 patients who ejaculated preoperatively, anterograde ejaculation was preserved in 81% with a gradual improvement in sperm volume. MSHQ scores also improved from 9 to 11.5 points during the 1 st year of follow-up.

These findings revealed a significant difference with respect to the standard Millin technique: in fact, the patients who underwent urethral-sparing adenomectomy reported a higher rate of anterograde ejaculation and a better score at MSHQ questionnaire at every time point (Table 3).

In other words, usRASP allows the same perioperative and urinary functional results as those of a standard Millin technique, while improving the outcome in terms of sexual function.

Concerning a specific subanalysis of the single items of the MSHQ-EjD-SF questionnaire in the urethral-sparing group, frequency of ejaculation and patients' global perception were implemented after the surgery.

It is important to note that with multivariable logistic regression at 3rd month postoperatively, younger age at surgery (OR 0.87, $p = 0.012$) and the absence of urethral infraction (OR 0.87, $p = 0.022$) were found to be predictors of ejaculation recovery, while at 12 mo it was influenced only by the age at surgery (OR 0.90, $p = 0.010$). This finding can be explained by the fact that in the first months postoperatively, the urethra underwent a remodeling process that can potentially cause edema or alter the urethra's physiological contractions during ejaculation.

Moreover, we note that the presence or not of a median lobe does not affect ejaculatory outcomes.

Finally, focusing on the perioperative data, our technique turned out to be safe, with only two major complications recorded. The median hospital stay was 5 (IQR 4–6) d, and the median catheterization time was 4 (IQR 3–6) d. We noticed that even in the case of a median lobe, where a cystotomy is required, no increase in catheterization, drainage time, hospital stay, or complications was recorded.

In the patients who underwent postoperative cystoscopy, no obstructions were observed at the prostatic urethra, and when the mp-MRI was performed, no residual adenoma was observed with physiological re-expansion of the prostatic capsule.

Nevertheless, the present study is not devoid of limitations. First, the duration of follow-up is still short, even if it is ongoing. Second, the lack of a standardized comparison cohort precludes definitive conclusions about the superiority of this technique over the available alternative options.

Despite these limitations, the results of this prospective study showed that urethral-sparing adenomectomy techniques are a safe and effective option for the treatment of large prostate adenomas, even in case of a median lobe, and allow for preservation of anterograde ejaculation in a vast majority of patients who ejaculated before the intervention.

5. Conclusions

Our study confirmed that usRASP is a safe and effective procedure that allows resolution of LUTS in patients with large BPH. Moreover this technique permits maintaining ejaculatory function in a large number of patients. This technique should be considered as an option when counseling patients with large BPH who are motivated to preserve antegrade ejaculation.

***Author contributions*:** Francesco Porpiglia 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: Porpiglia.
Acquisition of data: Niculescu, Volpi, De Cillis.
Analysis and interpretation of data: Piramide, Checcucci.
Drafting of the manuscript: Checcucci, Amparore, Porpiglia.
Critical revision of the manuscript for important intellectual content: Fiori, Manfredi, Autorino.
Statistical analysis: Checcucci, Piramide.
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Administrative, technical, or material support: None.
Supervision: Porpiglia.
Other: Amparore (drawings).

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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.2020.09.028 and via www.europeanurology.com.

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Prostate Cancer

External Validation and Addition of Prostate-specific Membrane Antigen Positron Emission Tomography to the Most Frequently Used Nomograms for the Prediction of Pelvic Lymph-node Metastases: an International Multicenter Study

Dennie Meijer[a,b,*], *Pim J. van Leeuwen*[c], *Matthew J. Roberts*[d,e,f], *Amila R. Siriwardana*[d], *Andrew Morton*[d,g], *John W. Yaxley*[d,g,h], *Hemamali Samaratunga*[g,i], *Louise Emmett*[j,k], *Peter M. van de Ven*[l], *Henk G. van der Poel*[c], *Maarten L. Donswijk*[m], *Thierry N. Boellaard*[n], *Ivo G. Schoots*[n], *Daniela E. Oprea-Lager*[b], *Geoffrey D. Coughlin*[g,h], *André N. Vis*[a,c]

[a] *Department of Urology, Prostate Cancer Network Netherlands, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands;* [b] *Department of Radiology & Nuclear Medicine, Cancer Center Amsterdam, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands;* [c] *Department of Urology, Prostate Cancer Network Netherlands, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [d] *Department of Urology, Royal Brisbane and Women's Hospital, Brisbane, Australia;* [e] *University of Queensland Centre for Clinical Research, Herston, Australia;* [f] *Department of Urology, Redcliffe Hospital, Brisbane, Australia;* [g] *Faculty of Medicine, University of Queensland, Brisbane, Australia;* [h] *Department of Urology, Wesley Hospital, Brisbane, Australia;* [i] *Department of Pathology, Aquesta Uropathology, Brisbane, Australia;* [j] *St. Vincent's Clinical School, University of New South Wales, Kensington, Australia;* [k] *Department of Theranostics and Nuclear Medicine, St. Vincent's Hospital Sydney, Darlinghurst, Australia;* [l] *Department of Epidemiology and Data Science, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands;* [m] *Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [n] *Department of Radiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

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Abstract

Background: Different nomograms exist for the preoperative prediction of pelvic lymph-node metastatic disease in individual patients with prostate cancer (PCa). These nomograms do not incorporate modern imaging techniques such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET).
Objective: To determine the predictive performance of the Briganti 2017, Memorial Sloan Kettering Cancer Center (MSKCC), and Briganti 2019 nomograms with the addition of PSMA-PET in an international, multicenter, present-day cohort of patients undergoing robot-assisted radical prostatectomy (RARP) and extended pelvic lymph-node dissection (ePLND) for localized PCa.
Design, setting, and participants: All 757 eligible patients who underwent a PSMA-PET prior to RARP and ePLND in three reference centers for PCa surgery between January 2016 and November 2020 were included.
Outcome measurements and statistical analysis: Performance of the three nomograms was assessed using the receiver operating characteristic curve–derived area under the curve (AUC), calibration plots, and decision curve analyses. Subsequently, recalibration and addition of PSMA-PET to the nomograms were performed.

* Corresponding author. De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
Tel. +31-20-4443289; Fax: +31-20-4446031. E-mail address: d.meijer2@amsterdamumc.nl

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Prostate-specific membrane antigen positron emission tomography imaging
Lymph-node metastases
Nomograms

Results and limitations: Overall, 186/757 patients (25%) had pelvic lymph-node metastatic (pN1) disease on histopathological examination. AUCs of the Briganti 2017, MSKCC, and Briganti 2019 nomograms were 0.70 (95% confidence interval [95% CI]: 0.64–0.77), 0.71 (95% CI: 0.65–0.77), and 0.76 (95% CI: 0.71–0.82), respectively. PSMA-PET findings showed a significant association with pN1 disease when added to the nomograms ($p < 0.001$). Addition of PSMA-PET substantially improved the discriminative ability of the models yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively. In decision curve analyses, the addition of PSMA-PET to the three nomograms resulted in increased net benefits.
Conclusions: The addition of PSMA-PET to the previously developed nomograms showed substantially improved predictive performance, which suggests that PSMA-PET is a likely future candidate for a modern predictive nomogram.
Patient summary: Different tools have been developed to individualize the prediction of prostate cancer spread to lymph nodes before surgery. We found that the inclusion of modern imaging (prostate-specific membrane antigen positron emission tomography) improved substantially the overall performance of these prediction tools.

1. Introduction

For patients with localized prostate cancer (PCa), robot-assisted radical prostatectomy (RARP) has become the most common curative surgical treatment option. It is generally accepted that extended pelvic lymph-node dissection (ePLND) is the gold standard staging method for the presence of pelvic lymph-node metastases (pN1 disease) and is recommended by international clinical practice guidelines in patients with unfavorable intermediate- and high-risk disease [1,2]. Whether to perform an ePLND is based on well-established preoperative nomograms, such as the Briganti 2017 nomogram [3], the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [4], or the Briganti 2019 nomogram [5]. The Briganti 2017 and MSKCC nomograms are both based on the same clinical, biochemical, and pathological preoperative variables, whereas the Briganti 2019 nomogram also incorporates imaging findings and targeted biopsy histology following multiparametric magnetic resonance imaging (mpMRI). The cutoff percentage above which an ePLND is advised, differs between 2% in the National Comprehensive Cancer Network guidelines [6], 5% in the European Association of Urology guidelines [1], and 7% in the Briganti 2019 nomogram [5].

The performance of these models, as quantified by the area under the curve (AUC), was found to be accurate in the original cohort studies, as well as on external validation [3–5]. However, these nomograms were based on data derived from patients who had their surgery prior to the increased adoption of modern imaging techniques such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT), for staging. The diagnostic accuracy of PSMA-PET was found to be significantly higher than that of conventional imaging techniques (ie, contrast-enhanced CT and bone scintigraphy) [7,8]. A recent subgroup analysis in the proPSMA study showed that the diagnostic accuracy of PSMA-PET for the detection of regional lymph-node and distant metastases was superior to that of conventional imaging [7]. Consequently, due to more accurate staging, PSMA-PET influences the characteristics of patients who are selected for curative surgery. As PSMA-PET is not incorporated in the validated and widely used nomograms, the potential benefits of modern imaging to enhance individualized prediction of pN1 disease are uncertain. Therefore, the aim of the present study was to evaluate the additive performance of PSMA-PET when incorporated in well-established preoperative nomograms to predict pelvic lymph-node metastases.

2. Patients and methods

2.1. Study design, and inclusion and exclusion criteria

We evaluated all patients who underwent PSMA-PET imaging, prior to RARP and ePLND in three reference centers for PCa surgery (ie, Amsterdam UMC and Netherlands Cancer Institute [both in Amsterdam, the Netherlands], and Wesley Hospital [Brisbane, Australia]) in two countries, between January 2016 and November 2020.

The study was approved by the institutional review board of the participating centers (VUmc2019.586, IRBd20-041, and UCH-HREC-2019.26.304, respectively). Patients were excluded from analyses when testosterone-lowering therapies were given before surgery.

2.2. Preoperative nomograms

Three nomograms for the prediction of pN1 disease were considered in our studied cohort. The Briganti 2017 and MSKCC nomograms were used for patients who did not undergo preoperative magnetic resonance imaging (MRI)-targeted biopsies or who had tumor-negative MRI-targeted biopsies [3,4]. The Briganti 2019 nomogram was applied in patients who had tumor-positive MRI-targeted biopsies of suspicious lesions (Prostate Imaging Reporting and Data System [PI-RADS] 3–5) on mpMRI [5].

For all included patients, preoperative parameters, relevant for either the Briganti 2017 nomogram [3] (ie, initial prostate-specific antigen [PSA] value, clinical T stage, biopsy grade group (GG), and percentage of positive cores with highest-grade and lower-grade PCa), the MSKCC nomogram [4] (ie, initial PSA value, clinical T stage, biopsy GG, and the

number of negative and positive cores), or the Briganti 2019 nomogram [5] (ie, initial PSA value, radiological T stage, lesion diameter on mpMRI, GG from MRI-targeted biopsies, and percentage of cores with clinically significant PCa) were registered.

Moreover, PSMA-PET findings were collected for each patient (molecular imaging [mi] N0: no evidence of pelvic lymph-node metastases; miN1: at least one pelvic lymph-node metastasis).

2.3. Multiparametric MRI imaging

Radiological staging was based on the mpMRI findings, using the PI-RADS v2.0 and, since 2019, v2.1 [9]; rT1c was classified as PI-RADS ≤2 scores, rT2 if a PI-RADS 3–5 lesion showed no extracapsular extension (ECE), rT3a if there was evidence of ECE on mpMRI, and rT3b if there was evidence of seminal vesicle invasion. All scans were reported by expert radiologists.

2.4. PSMA-PET imaging

All PSMA-PET scans were either performed or clinically revised in high-volume PCa surgery centers according to local protocol. The vast majority of the PSMA-PET scans was performed when biopsy GG 3 or any other high-risk parameter was present, such as an initial PSA value of ≥20 ng/ml, or clinical or radiological ≥T3 disease. At an on-site cyclotron facility, ^{18}F-DCFPyL and ^{18}F-PSMA-1007 were synthesized via direct radiofluoration, whereas ^{68}Ga-PSMA-11 was produced on site, compliant to the Good Manufacturing Practices guidelines. PET images were made from mid-thigh to skull base: median 120 min (interquartile range [IQR] 90–120) after injection following a median dose of 299 MBq (IQR 222–317) for ^{18}F-DCFPyL, 51 min (IQR 45–60) after injection following a median dose of 114 MBq (IQR 97–158) for ^{68}Ga-PSMA-11, and approximately 90 min after injection following a median dose of 284 MBq (IQR 245–308) for ^{18}F-PSMA-1007. PET images were combined with a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation), a diagnostic CT scan (130 kV, 110 mAs), or MRI for anatomical correlation. All PET images were corrected for scatter, decay, and random coincidences; attenuation correction was performed using CT or MRI images.

All PSMA-PET scans were discussed in a multidisciplinary meeting attended by at least one highly experienced nuclear medicine physician. According to the PROMISE criteria [10], locoregional lymph-node metastases on PSMA-PET were defined as lymph nodes in the true pelvis.

2.5. Extended pelvic lymph-node dissection and histopathological evaluation

All ePLNDs were performed by experienced urological surgeons affiliated with one of the participating institutions. A bilateral ePLND was performed up to and including the crossing between the ureter and common iliac vessels, along the external iliac vessels, including the lymph nodes lateral to the internal iliac vessels and within the obturator fossa. Lymph-node specimens were examined by high-volume, committed uropathologists according to International Society of Urological Pathology (ISUP) protocols [11,12]. The pelvic lymph nodes and associated fat were blocked, and the total lymph-node count included palpable nodes, in addition to microscopically identifiable nodes. A pathological lymph-node assessment, either pN0 or pN1, was given for each case.

2.6. Outcome variables and statistical analysis

The ability of the three nomograms to discriminate between patients with and without pN1 disease was quantified by the AUC. Calibration plots were made to assess the agreement between predicted and observed risks for pN1 disease. To this end, patients were grouped based on the deciles of the predicted risks. Subsequently, the average observed risk was plotted against the average predicted risk for each of the ten groups. Decision curve analyses (DCAs) were used to visualize the net benefit of the three nomograms as a function of the threshold probability [13]. The threshold probability reflects the variation in predicted risks that patients or doctors consider minimally required in order to undergo or perform a specific intervention. The net benefit of a nomogram is that it correctly identifies which patients have and who do not have pN1 disease. The unit of net benefit is the proportion of true positives as a fraction of the target population. Predictive performance of the original nomograms was assessed by calculation of AUCs, calibration plots, and performing a DCA. PSMA-PET findings were incorporated in the nomograms using logistic regression, with pN1 disease as outcome and PSMA-PET findings and the linear predictor of the original nomogram as independent variables. AUCs and DCAs for models with PSMA-PET, corrected for overoptimism, were obtained using a ten-fold cross-validation procedure. Original models were recalibrated to facilitate a comparison of predictive performance with models with PSMA-PET incorporated. Model recalibration was done through re-estimation of intercept and slope. To this end, linear predictors for the original models were calculated using coefficients as published and subsequently used as the single independent variable in a logistic regression analysis with pelvic lymph-node metastatic (pN1) disease as outcome. DCAs for these recalibrated original models were also corrected for overoptimism using ten-fold cross-validation. As suggested by Demler et al [14], we first tested the association of the additional predictor PSMA-PET with pN1 disease using logistic regression and,

Table 1 – Preoperative characteristics of all included patients who underwent RARP and ePLND

	All included patients (*n* = 757)
Age at surgery (yr), median (IQR)	67 (62–71)
Initial PSA value (ng/ml), median (IQR)	9.6 (6.4–18.7)
Biopsy grade group according to ISUP, *n* (%)	
1	22 (3)
2	119 (16)
3	170 (22)
4	218 (29)
5	228 (30)
EAU risk group, *n* (%)	
Low risk	2 (<1)
Intermediate risk	179 (24)
High risk	576 (76)
mpMRI findings, *n* (%)	
No mpMRI performed	69 (9)
Radiological T stage, *n* (%)	
Negative (rT1c)/organ-confined disease (rT2)	403 (53)
Extracapsular extension (rT3a)	166 (22)
≥Seminal vesicle invasion (rT3b)	119 (16)
PI-RADS score, *n* (%)	
1–2	33 (4)
3–5	655 (87)
PSMA-PET findings, *n* (%)	
miN0	653 (86)
miN1	104 (14)

EAU = European Association of Urology; ePLND = extended pelvic lymph-node dissection; IQR = interquartile range; ISUP = International Society of Urological Pathology; mi = molecular imaging; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RARP = robot-assisted radical prostatectomy.

when significant, reported the change in AUC with the corresponding 95% confidence interval (95% CI).

To obtain predicted risks for patients with missing variables (n = 65), a multiple imputation procedure was conducted. The imputation model consisted of initial PSA value, biopsy GG, clinical T stage, information on biopsy cores, and, if available, mpMRI findings, and ten imputed datasets were created. Afterward, missing values were replaced by the mean of the imputed values. Predicted risks were subsequently calculated on the complete dataset. Analyses were performed in Stata version 14 (StataCorp, College Station, TX, USA).

3. Results

3.1. Preoperative baseline characteristics

A total of 757 patients were included. All men underwent RARP and ePLND at a median initial PSA value of 9.6 ng/ml (IQR 6.4–18.7), with a median age of 67 yr (IQR 62–71; Table 1). No differences in baseline characteristics were observed between patients with complete data and those with missing data (Supplementary Table 1).

3.2. Imaging prior to RARP

Multiparametric MRI was performed in 688 patients (91%). PSMA-PET was performed in all included patients, of whom 653 (86%) had miN0 on PSMA-PET and 104 (14%) had miN1 (Table 1).

3.3. Final histopathological examination

Of all 757 included patients, 571 (75%) had no evidence of lymph-node metastatic disease (pN0), whereas 186 (25%) had pN1 disease (Table 2). The median number of resected lymph nodes was 18 (IQR 13–24).

The sensitivity, specificity, positive predictive value, and negative predictive value of PSMA-PET for the detection of pN1 disease were 38%, 94%, 68%, and 82%, respectively. The median size of pelvic lymph-node metastases detected by preoperative PSMA-PET (miN1) was 6 mm (IQR 4–10) compared with 3 mm (IQR 2–5) in patients who were negative for lymph-node metastases (miN0) on preoperative PSMA-PET (Mann-Whitney; $p < 0.001$).

3.4. Preoperative risk assessment

In total, 418/757 patients (55%) did not undergo MRI (n = 69), did not undergo MRI-targeted biopsies (n = 341), or did not have tumor-positive MRI-targeted biopsies (n = 8), and therefore the Briganti 2017 and MSKCC nomograms were applied. Based on the Briganti 2017 nomogram, 153/418 patients (37%) were predicted to have pN1 disease. Based on the MSKCC nomogram, 106/418 patients (25%) were predicted to have pN1 disease. The observed number of patients with pN1 disease in this cohort was 96/418 (23%).

For patients who had tumor-positive MRI-targeted biopsies (n = 339), the Briganti 2019 nomogram was applied. Of these 339 patients, 91 (27%) were predicted to have pN1 disease. The observed number of patients with pN1 disease in this cohort was 90/339 (27%).

3.5. Performance of original nomograms

The calibration plots of the Briganti 2017, MSKCC, and Briganti 2019 nomograms are shown in Figure 1. The Briganti 2017 nomogram underestimated the risk of pN1 disease in the present cohort in low ranges (predicted risks <10%) and overestimated the risk of pN1 in higher ranges (predicted risks >10%). Using the MSKCC nomogram, the expected risk of pN1 disease was underestimated in the studied cohort in low ranges (predicted risks <10%), whereas this risk was overestimated in the patients with a predicted risk of pN1 disease of >50%. AUCs of the Briganti 2017 and MSKCC nomograms were 0.70 (95% CI: 0.64–0.76) and 0.71 (95% CI: 0.65–0.77), respectively. The AUCs stratified for patients with miN0

Table 2 – Final histopathological results of all included patients who underwent RARP and ePLND

	pN0 disease (n = 571)	pN1 disease (n = 186)
Pathological T stage, n (%)		
pT2	258 (45)	15 (8)
pT3a	225 (39)	60 (32)
pT3b	287 (15)	109 (59)
pT4	1 (<1)	2 (1)
Specimen grade group according to ISUP, n (%)		
1	6 (1)	1 (<1)
2	190 (33)	18 (10)
3	192 (34)	57 (31)
4	40 (7)	16 (9)
5	143 (25)	94 (50)
Surgical margin status, n (%)		
Negative	405 (71)	86 (46)
Positive	165 (29)	100 (54)
Missing [a]	1 (<1)	0 (0)
Number of removed lymph nodes, median (IQR)	19 (14–24)	20 (15–26)

ePLND = extended pelvic lymph-node dissection; IQR = interquartile range; ISUP = International Society of Urological Pathology; RARP = robot-assisted radical prostatectomy.

[a] Pathologist was not able to define the surgical margin status.

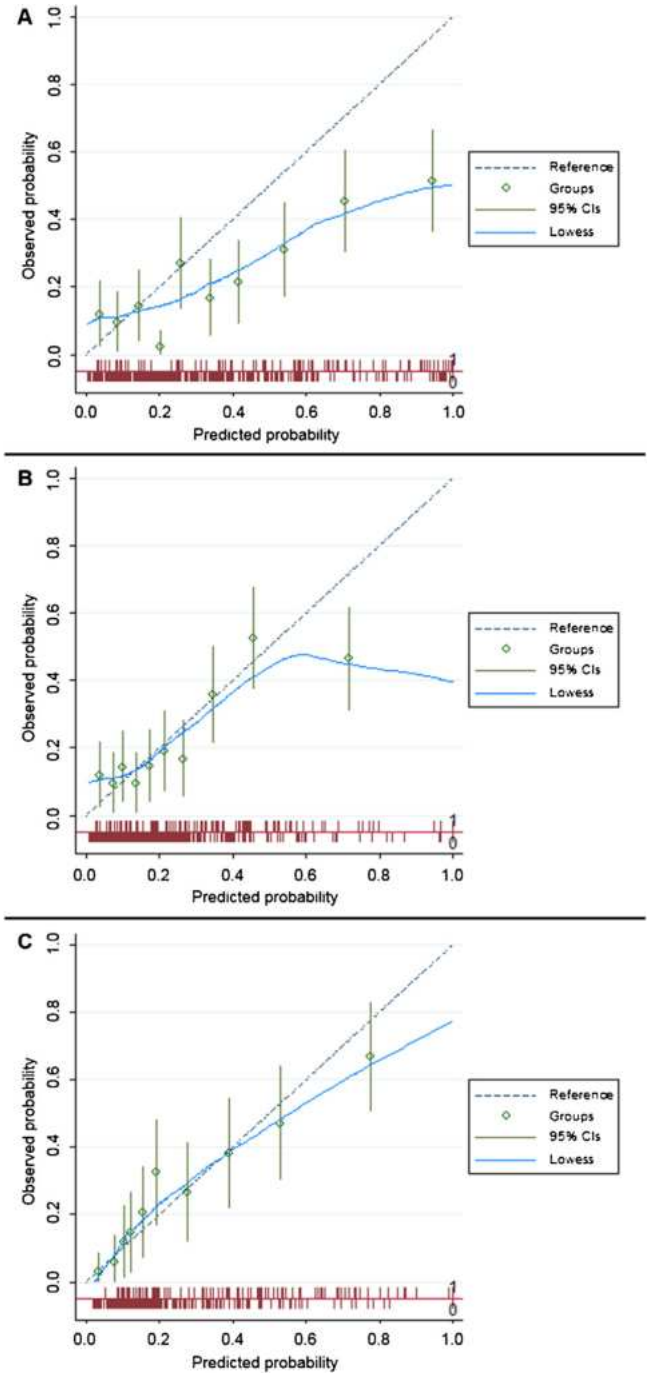

Fig. 1 – Calibration plots of the (A) Briganti 2017 nomogram on the present population (*n* = 418), (B) MSKCC nomogram on the present population (*n* = 418), and (C) Briganti 2019 nomogram on the present population (*n* = 339). CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center.

versus miN1 on PSMA-PET can be found in Supplementary Table 2. The calibration plot of the Briganti 2019 nomogram showed good calibration over the whole range of predicted risks, although larger predicted risks (predicted risks >50%) tended to overestimate observed risks. The AUC of the Briganti 2019 nomogram was 0.76 (95% CI: 0.71–0.82).

The DCA for the Briganti 2017 nomogram showed a positive net benefit for pN1 risks between 15% and 35% (Fig. 2A). After recalibration, a positive net benefit was observed for pN1 risks between 15% and 40%. The DCA for the MSKCC nomogram showed a positive net benefit for pN1 risks between 15% and 35% (Fig. 2B). After recalibration, a positive net benefit was observed for pN1 risks between 15% and 40%. The DCA for the Briganti 2019 nomogram showed a positive net benefit for pN1 risks between 10% and 40% for both the original and the recalibrated nomogram (Fig. 2C).

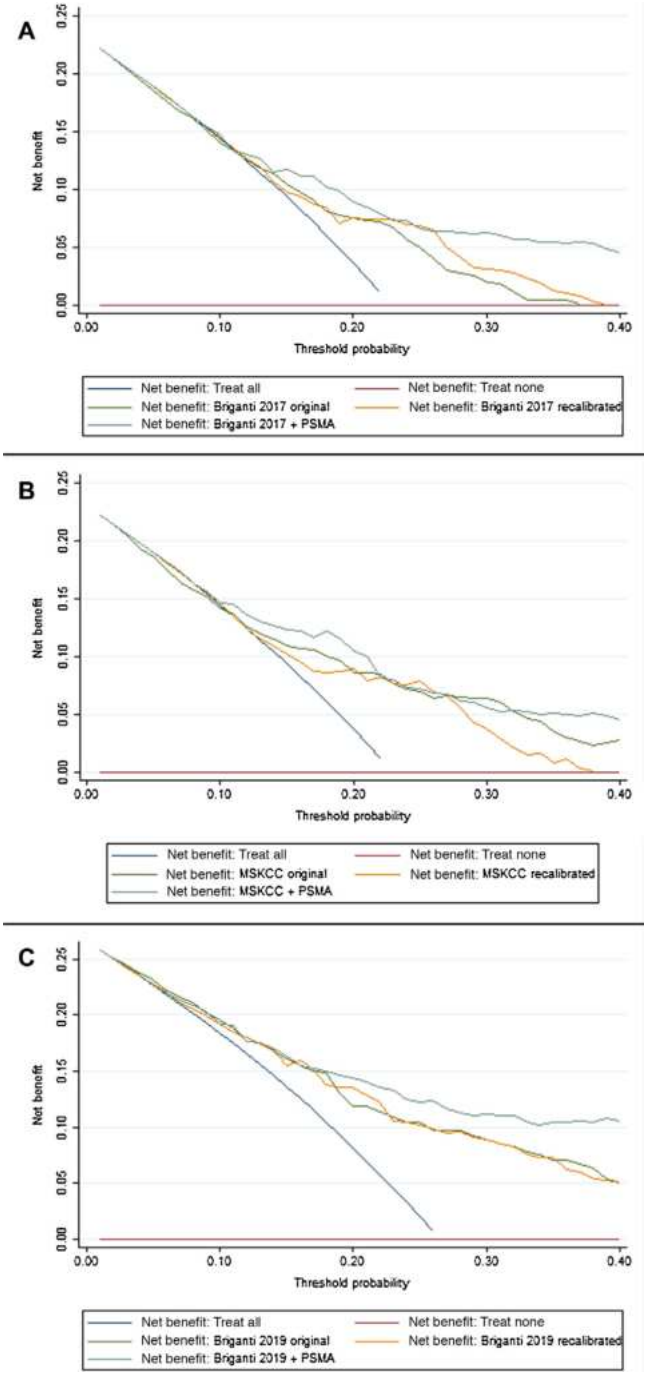

Fig. 2 – Decision curve analyses of the (A) Briganti 2017 nomogram on the present population (*n* = 418; original model, recalibrated model, recalibrated + addition of PSMA-PET), (B) MSKCC nomogram on the present population (*n* = 418; original model, recalibrated model, recalibrated + addition of PSMA-PET), and (C) Briganti 2019 nomogram on the present population (*n* = 339; original model, recalibrated model, recalibrated + addition of PSMA-PET). MSKCC = Memorial Sloan Kettering Cancer Center; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

3.6. Performance of nomograms after addition of PSMA-PET

Odds ratios for miN1 on PSMA-PET when added to the linear predictors of the original Briganti 2017, MSKCC, and Briganti 2019 nomograms were 8.1 (95% CI: 4.3–15.3, $p < 0.001$), 8.7 (95% CI: 4.6–16.5, $p < 0.001$), and 13.3 (95% CI: 6.1–29.2, $p < 0.001$), respectively. When PSMA-PET was added to the nomograms, the AUCs increased to 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively (Fig. 3 and Table 3). Increases in AUCs were, respectively, 0.053 (95% CI: 0.008–0.098), 0.065 (95% CI: 0.016–0.11), and 0.052 (95% CI: 0.014–0.091). DCAs showed that addition of PSMA-PET to the present cohort resulted in nomograms with a positive net benefit for pN1 risks

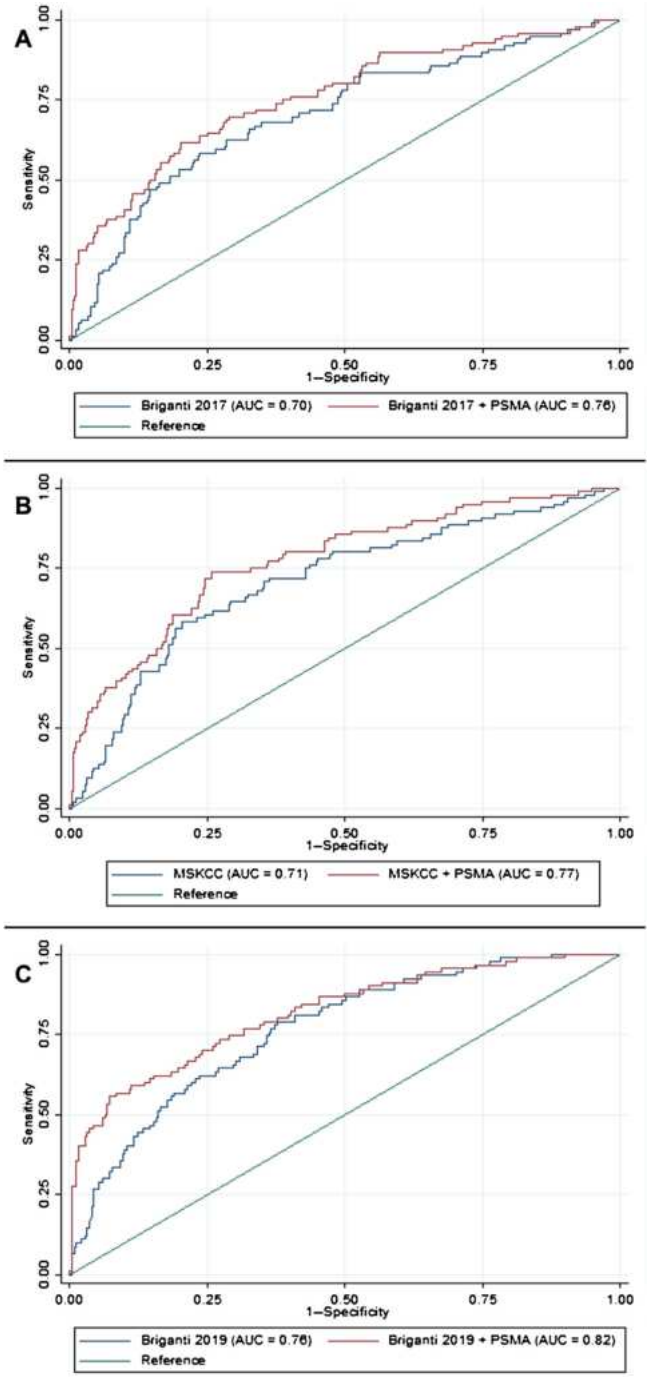

Fig. 3 – ROC curves of the (A) Briganti 2017 nomogram on the present population (*n* = 418; original model, model with the addition of PSMA-PET), (B) MSKCC nomogram on the present population (*n* = 418; original model, model with the addition of PSMA-PET), and (C) Briganti 2019 nomogram on the present population (*n* = 339; original model, model with the addition of PSMA-PET). AUC = area under the curve; MSKCC = Memorial Sloan Kettering Cancer Center; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; ROC = receiver operating characteristic.

between 10% and 40% for all three nomograms (Fig. 2). Clarity regarding the clinical implications of these findings can be found in Supplementary Table 3. Per cutoff, the number of potential patients in whom an ePLND can be spared is noted, along with the number of metastases missed (pN1) and the number of correctly omitted ePLNDs (pN0).

4. Discussion

In a multicenter, international population that underwent RARP and ePLND, we evaluated the performance of three well-established preoperative models (ie, the Briganti 2017 [3], MSKCC [4], and Briganti 2019 nomograms [5]) for predicting pN1 disease and assessed whether PSMA-PET

Table 3 – Performance of the different preoperative nomograms in the present population, both with and without the addition of PSMA-PET findings

	AUC (95% CI) without PSMA-PET	AUC (95% CI) with PSMA-PET findings
Briganti 2017	0.70 (0.64–0.77)	0.76 (0.70–0.82)
MSKCC	0.71 (0.65–0.77)	0.77 (0.72–0.83)
Briganti 2019	0.76 (0.71–0.82)	0.82 (0.76–0.87)

AUC = area under the curve; CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Center; PSMA = prostate-specific membrane antigen; PET = positron emission tomography.
Recalibration of models by re-estimation of slope and intercept does not affect AUCs, and the AUCs given for models without PSMA-PET therefore apply to both the original and the recalibrated model.

imaging was able to improve the performance of these models.

Overall, we found that the predictive performance of the Briganti 2017, MSKCC, and Briganti 2019 nomograms improved significantly when PSMA-PET findings were added to the models. Practically, this implies that preoperative nomograms predict the outcome of ePLND more accurately when PSMA-PET imaging is available. It may be proposed that patients who are deemed candidates for radical surgery need preoperative PSMA-PET to counsel them more adequately on the risk of having pN1 disease. Moreover, using PSMA-PET imaging allows for more accurate localization of pelvic lymph-node metastases.

We further demonstrated that when our population was used as a validation cohort for the three preoperative models, the AUCs for predicting pN1 disease were substantially lower than those of the cohorts on which the nomograms were originally based [5]. Especially in patients with miN0 on preoperative PSMA-PET, in whom an accurate nomogram is even more critical, the AUCs of the nomograms on the present cohort were insufficient. Therefore, apparently, currently applied predictive nomograms do not perform as well in our present-day population as in the original cohorts. The differences in the reported AUCs of these nomograms may well be explained by differences in the baseline characteristics of the original cohort compared with those of ours, particularly with respect to tumor aggressiveness features. These differences in baseline features may be caused by today's tendency to enroll patients with low-stage, low-grade disease into active surveillance protocols. Moreover, due to surgical improvements, increased dexterity, and familiarity with the procedure, more patients with higher stages and higher grades of disease undergo surgical treatment for PCa [15]. Furthermore, as all included patients underwent preoperative PSMA-PET imaging, the relative proportion of patients with unfavorable tumor features is likely higher than the proportions reported previously, as reflected by the increased presence of pelvic lymph-node metastases after surgery (ie, 12.5% in the population of the Briganti 2019 nomogram vs 24.5% in our population).

As visualized in the calibration plots (Fig. 1A and 1B), both the Briganti 2017 and the MSKCC nomogram underestimate the risk of pN1 disease in the expected percentages of 0–10%. This means that in the cohort of patients with a low expected risk of pN1 disease, according to conventional nomograms, the observed risk of pN1 disease may be 10–20% higher than expected. This may be particularly worrisome for patients who have an expected risk that falls below the cutoff value to discriminate between ePLND and no ePLND, usually below 5–7% according to most international guidelines [1,2,6]. In these cases, despite recommendation to refrain from ePLND, a substantial proportion of patients may still experience pN1 disease.

The Briganti 2019 nomogram seems to be calibrated accurately on the data of the present-day surgically treated cohort. Recently, several studies validated the Briganti 2019 nomogram [16,17], which confirmed the good performance of this nomogram. Unfortunately, this model is applicable only in patients in whom lesions are suspicious on mpMRI and who subsequently have tumor-positive MRI-targeted biopsies. Previous studies have shown that a PCa diagnosis is made on systematic biopsies instead of on MRI-targeted biopsies in a substantial proportion of patients in whom prostate biopsy is prompted [18]. These patients, by definition, are not eligible for the Briganti 2019 nomogram. Furthermore, not all clinics perform MRI-targeted biopsies as standard of care currently. For these patients, an accurate model for predicting pN1 disease prior to RARP is warranted.

Our study is not devoid of limitations. First, it should be noted that all PSMA-PET scans were reported in routine clinical settings and were not part of a prospective clinical trial. Therefore, different scan protocols and PET scanners were used. Second, multiple surgeons performed RARP and ePLND, and multiple pathologists reported on the histopathology in the RARP and ePLND specimens, although the median node count removed at ePLND is consistent with international standards [19], and the histopathology reporting was performed in high-volume experienced uropathology laboratories. It is possible that a difference in the extent and technique of ePLND between surgeons, and the identification of pN1 disease on histopathological examination, could have influenced the results.

5. Conclusions

We validated the Briganti 2017, MSKCC, and Briganti 2019 nomograms that were originally developed for the prediction of lymph-node involvement in an international, multicenter, surgically treated cohort of patients with clinically localized PCa. The addition of PSMA-PET to previously developed nomograms showed substantially

improved performance in predicting the outcome of ePLND correctly, which suggests that PSMA-PET is a likely future candidate for a modern predictive nomogram.

Author contributions: Dennie Meijer 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: Meijer, van Leeuwen, Roberts, Vis.
Acquisition of data: Meijer, van Leeuwen, Roberts, Siriwardana, van der Poel, Coughlin, Vis.
Analysis and interpretation of data: Meijer, van Leeuwen, Roberts, van de Ven, Vis.
Drafting of the manuscript: Meijer, van Leeuwen, Roberts, van de Ven, Vis.
Critical revision of the manuscript for important intellectual content: Siriwardana, Morton, Yaxley, Samaratunga, Emmett, van der Poel, Donswijk, Boellaard, Schoots, Oprea-Lager, Coughlin.
Statistical analysis: Meijer, van de Ven.
Obtaining funding: None.
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Supervision: van Leeuwen, Roberts, Vis.
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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.2021.05.006.

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Prostate Cancer

Elucidating Prostate Cancer Behaviour During Treatment via Low-pass Whole-genome Sequencing of Circulating Tumour DNA

Semini Sumanasuriya[a,b,†], *George Seed*[a,†], *Harry Parr*[a], *Rossitza Christova*[a], *Lorna Pope*[a], *Claudia Bertan*[a], *Diletta Bianchini*[a,b], *Pasquale Rescigno*[a,b], *Ines Figueiredo*[a], *Jane Goodall*[a], *Gemma Fowler*[a], *Penelope Flohr*[a], *Niven Mehra*[a,b], *Antje Neeb*[a], *Jan Rekowski*[a], *Mario Eisenberger*[c], *Oliver Sartor*[d], *Stéphane Oudard*[e], *Christine Geffriaud-Ricouard*[f], *Ayse Ozatilgan*[f], *Mustapha Chadjaa*[f], *Sandrine Macé*[f], *Chris Lord*[g], *Joe Baxter*[g], *Stephen Pettitt*[g], *Maryou Lambros*[a,b], *Adam Sharp*[a,b], *Joaquin Mateo*[h], *Suzanne Carreira*[a,b], *Wei Yuan*[a,b], *Johann S. de Bono*[a,b,*]

[a] *The Institute of Cancer Research, University of London, London, UK;* [b] *The Royal Marsden Hospital, London, UK;* [c] *Johns Hopkins University, Baltimore, MD, USA;* [d] *Tulane Medical School, New Orleans, LA, USA;* [e] *Hôpital Européen Georges Pompidou and Université de Paris, Paris, France;* [f] *Sanofi-Genzyme, Paris, France;* [g] *The CRUK Gene Function Laboratory and Breast Cancer Now Research Centre, The Institute of Cancer Research, London, UK;* [h] *Vall d'Hebron Institute of Oncology, Barcelona, Spain*

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Abstract

Background: Better blood tests to elucidate the behaviour of metastatic castration-resistant prostate cancer (mCRPC) are urgently needed to drive therapeutic decisions. Plasma cell-free DNA (cfDNA) comprises normal and circulating tumour DNA (ctDNA). Low-pass whole-genome sequencing (lpWGS) of ctDNA can provide information on mCRPC behaviour.
Objective: To validate and clinically qualify plasma lpWGS for mCRPC.
Design, setting, and participants: Plasma lpWGS data were obtained for mCRPC patients consenting to optional substudies of two prospective phase 3 trials (FIRSTANA and PROSELICA). In FIRSTANA, chemotherapy-naïve patients were randomised to treatment with docetaxel (75 mg/m^2) or cabazitaxel (20 or 25 mg/m^2). In PROSELICA, patients previously treated with docetaxel were randomised to 20 or 25 mg/m^2 cabazitaxel. lpWGS data were generated from 540 samples from 188 mCRPC patients acquired at four different time points (screening, cycle 1, cycle 4, and end of study).
Outcome measurements and statistical analysis: lpWGS data for ctDNA were evaluated for prognostic, response, and tumour genomic measures. Associations with response and survival data were determined for tumour fraction. Genomic biomarkers including large-scale transition (LST) scores were explored in the context of prior treatments.
Results and limitations: Plasma tumour fraction was prognostic for overall survival in univariable and stratified multivariable analyses (hazard ratio 1.75, 95% confidence interval 1.08–2.85; $p = 0.024$) and offered added value compared to existing biomarkers (C index 0.722 vs 0.709; $p = 0.021$). Longitudinal changes were associated with drug response. PROSELICA samples were enriched for LSTs ($p = 0.029$) indicating genomic instability, and this enrichment was associated with prior abiraterone and enzalutamide

† These authors contributed equally to this work and are joint lead authors.
* Corresponding author. The Institute of Cancer Research, 15 Cotswold Road, London SM2 5NG, UK. Tel. +44 208 7224029; Fax: +44 208 6427979.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

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treatment but not taxane or radiation therapy. Higher LSTs were correlated with losses of *RB1*/*RNASEH2B*, independent of *BRCA2* loss.
Conclusions: Plasma lpWGS of ctDNA describes CRPC behaviour, providing prognostic and response data of clinical relevance. The added prognostic value of the ctDNA fraction over established biomarkers should be studied further.
Patient summary: We studied tumour DNA in blood samples from patients with prostate cancer. We found that levels of tumour DNA in blood were indicative of disease prognosis, and that changes after treatment could be detected. We also observed a "genetic scar" in the results that was associated with certain previous treatments. This test allows an assessment of tumour activity that can complement existing tests, offer insights into drug response, and detect clinically relevant genetic changes.

1. Introduction

Prostate cancer (PC) remains a major cause of male cancer deaths [1] despite significant advances in systemic treatment [2]. Taxanes improve overall survival (OS) and provide symptomatic benefit from metastatic castration-resistant PC (mCRPC) [3,4] but uncertainty remains regarding how long to continue treatment, with early prostate-specific antigen (PSA) changes unable to guide treatment switch decisions. Better biomarkers of response are needed for early discontinuation of ineffective treatment. Measurement of total circulating cell-free DNA (cfDNA) in serial plasma samples is prognostic but is challenged by nonmalignant circulating DNA. The fraction of cfDNA that is tumour-derived—circulating tumour DNA (ctDNA)—can be estimated via next-generation sequencing to generate quantitative [5] and qualitative data [6], with serial ctDNA genomics providing important insights into disease behaviour and evolution [7].

Low-pass whole-genome sequencing (lpWGS) assesses genome-wide copy number events [8], allowing rapid, high-throughput, inexpensive testing of ctDNA and estimation of cfDNA tumour fraction, ploidy, and whole-genome copy number alterations (CNAs). lpWGS can characterise the impact of DNA repair defects and genomic instability by detailing copy-number fragment size and frequency, including large-scale transitions (LSTs) and tandem duplications [9–11]. Homologous repair scores, to which LSTs contribute, have been linked to PARP inhibitor sensitivity, and tandem duplication CNA genotypes reflect deleterious *CDK12* alterations that sensitise the individual to immunotherapy [10,12].

We validated a cfDNA lpWGS assay and tested samples from mCRPC patients treated in two taxane phase 3 trials, FIRSTANA (NCT01308567) and PROSELICA (NCT01308580). In FIRSTANA, chemotherapy-naïve patients were randomised to docetaxel (75 mg/m^2) or cabazitaxel (20 or 25 mg/m^2); in PROSELICA, docetaxel-pretreated patients were randomised to 20 or 25 mg/m^2 cabazitaxel [13,14]. Here we present lpWGS data from patients consenting to these extra analyses and clinical qualification that this biomarker provides prognostic and response data as well as information on evolving progressing disease.

2. Patients and methods

2.1. Patients and sample collection

Supplementary Figure 1 shows an outline of our study, while Supplementary Figure 2A,B shows overviews of the FIRSTANA and PROSELICA trials. Both trials have already been reported [13–15]. OS was defined as the time from randomisation to death from any cause. Patients who did not have an event were censored at the date of last contact. Radiographic and PSA progression-free survival (rPFS and PSA-PFS) were defined as the time from randomisation to the date of tumour progression.

To determine progression and response status we used Response Evaluation Criteria in Solid Tumours 1.1 and Prostate Cancer Working Group 2 Criteria, as previously described in the FIRSTANA and PROSELICA reports [13–15]. Studies on ctDNA were prospectively included as an optional exploratory endpoint in both trials. Clinical data included PSA, lactate dehydrogenase, haemoglobin, serum albumin, alkaline phosphatase, and Eastern Cooperative Oncology Group performance status. Plasma was collected from patients consenting to this substudy at two baseline time points 1–4 wk apart (at screening [SCR] and cycle 1 day 1 [C1]) and at cycle 4 day 1 (C4) and at the end of the study (EOS). Blood was collected in lithium heparin tubes (BD Vacutainer; BD Biosciences, San Jose, CA, USA). Plasma was collected from healthy volunteers (n = 10) and pooled prior to lpWGS. Biopsies were collected according to a prospective PC molecular characterisation protocol approved by the institutional review board [16].

2.2. cfDNA extraction and quantification

cfDNA was isolated from 1–4 ml of plasma using a QIAamp Circulating Nucleic Acid kit (Qiagen, Hilden, Germany). Of the 60 μl of eluate, 3 μl was used for quantification via a Quant-IT Picogreen HS DNA kit (ThermoFisher, Waltham, MA, USA) and concentrations were read on a BioTek microplate spectrophotometer (excitation 480 nm, emission 520 nm) (BioTek Instruments, Winooski, VT, USA).

2.3. Library preparation and sequencing

Following extraction, samples were treated with heparinase I (Sigma-Aldrich, St. Louis, MO, USA) [17]. Low-pass whole-genome library preparation was carried out using a Qiagen QiaSeq FX DNA library kit (Qiagen). Samples were sequenced on an Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Technical replicates were prepared and sequenced on an Illumina MiSeq system (Illumina) [18].

2.4. Bioinformatics processing

lpWGS data were converted to paired-end reads (bcl2fastq2 v.2.17.1.14) with default settings and subsequently aligned to the human reference genome (GRCh37) using the BWA-MEM (version 0.7.12) algorithm [33]. Quality control checks were performed using Picard (Broad Institute, Cambridge, MA, USA, version 2.8.1) and FASTQC (Babraham Institute, Babraham, UK, version 0.11.8). Samples were excluded from analysis if the sequencing depth was less than 0.05× or if they failed the FASTQC read quality filter. Aligned reads were quantified using HMMcopy readCounter [35] (version 0.99.0) with the quality filter and interval width set to 20 and 500 kb, respectively.

Read depth data were modelled and the tumour fraction was calculated using ichorCNA (version 0.1.0) [19]. Transition strength parameters were set at –txnE = 0.99999 and –txnStrength = 100000; the maximum copy number (CN) was set to 20 to account for amplifications. The germline DNA fraction (initial values 40% and 90%), ploidy (initial values 2 and 3), and subclonality were modelled. The default 500-kb reference coverage data set supplied with ichorCNA was used.

2.5. Data handling and statistical analyses

IchorCNA provides segmented CN data and estimates of tumour fraction and ploidy. These were further processed to generate both CN calls and LST values, as described in the Supplementary material [20]. Cox proportional-hazards models were used for multivariable survival analysis, and Kaplan-Meier curves for univariable survival comparisons. The log-likelihood test was used to compare regression models. Multivariable generalised linear and logistic regressions were used to study continuous and binary outcomes, respectively. A full listing of the regression variables is provided in the Supplementary material. Comparisons of continuous variables (tumour fraction and LST scores) between groups (study subset, prior treatment, specific CN events) in violin plots used the Wilcoxon rank-sum (unpaired data) or signed-rank (paired data) tests. Elastic-net regression was performed using eNetXplorer (version 1.1.0) [21], for which parameter selections are presented in the Supplementary material. Following elastic-net regression, significant ($p < 0.05$) bins were merged with adjacent highly correlated (Pearson's $r > 0.9$) bins to form merged regions for subsequent analyses, with the CN values of the most significant overlapping bin assigned to each final merged region.

3. Results

3.1. FIRSTANA and PROSELICA cohorts providing plasma samples for lpWGS

lpWGS data were generated from 540 samples acquired at four time points (SCR and C1, representing baseline, and C4 and EOS). Samples with plasma available after other preplanned analyses were tested, including 299 FIRSTANA (104 SCR, 55 C1, 79 C4, and 61 EOS) and 241 PROSELICA (84 SCR, 34 C1, 59 C4, and 64 EOS) samples. The

Table 1 – Baseline characteristics of the cohorts with castration-resistant prostate cancer from the FIRSTANA and PROSELICA studies

Characteristic	FIRSTANA (n = 103)	PROSELICA (n = 85)	p value
ECOG PS ≥2, n (%) [b]	3 (2.9)	10 (12)	0.02 [a]
RECIST-measurable, n (%) [b]	54 (52)	45 (53)	0.9 [a]
Visceral disease, n (%)	20 (19)	25 (29)	0.11 [a]
Pain at baseline, n (%) [c]	69 (67)	59 (69)	0.4 [a]
Gleason score <8 at diagnosis, n (%) [d]	42 (41)	45 (53)	0.051 [a]
Prior Abi/Enza treatment, n (%)	2 (1.9)	29 (35)	<0.001 [a]
Trial arm, n (%)			
Cabazitaxel (20 mg/m^2)	34 (33)	41 (48)	
Cabazitaxel (25 mg/m^2)	28 (27)	44 (52)	
Docetaxel (75 mg/m^2)	41 (40)	0 (0)	
Median age, yr (IQR)	68.0 (62.5–72.0)	67 (64.0–71.0)	0.2 [e]
Median LDH, U/l (IQR)	267 (204–360)	366 (234–605)	0.003 [e]
Median ALP, U/l (IQR)	129 (81.0–242)	214 (118–413)	0.002 [e]
Median haemoglobin, g/dl (IQR)	121 (111–128)	112 (105–122)	<0.001 [e]
Median albumin, g/dl (IQR)	40.2 (37.5–43.4)	40.0 (36.0–43.0)	0.2 [e]
Median PSA, ng/ml (IQR)	60.4 (18.2–188)	161 (64.9–623)	<0.001 [e]
Median PSA doubling time, d (IQR)	62 (36–100)	51 (35–86)	0.3 [e]
Median NLR (IQR)	2.25 (1.53–4.10)	2.79 (1.69–3.89)	0.17 [e]
Outcomes			
>50% PSA response at 12 wk, n (%)	55 (53)	23 (27)	<0.001 [a]
>50% PSA response at any time, n (%)	68 (66)	33 (39)	<0.001 [a]
Median OS, mo (95% CI)	21.3 (17.2–23.9)	13.3 (11.5–15.8)	<0.001 [f]
Median rPFS, mo (95% CI)	11.6 (9.86–13.6)	7.13 (6.11–12.4)	0.003 [f]
Median PSA-PFS, mo (95% CI)	7.43 (6.64–8.94)	4.86 (4.14–7.29)	0.003 [f]
Censored (n)	30	6	
Median FU for censored patients (mo)	32.0	Insufficient cases	

Abi = abiraterone; ALP = alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group performance status; Enza = enalutamide; FU = follow-up; IQR = interquartile range; LDH = lactate dehydrogenase; NLR = neutrophil/lymphocyte ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = radiographic PFS.

[a] χ^2 test.

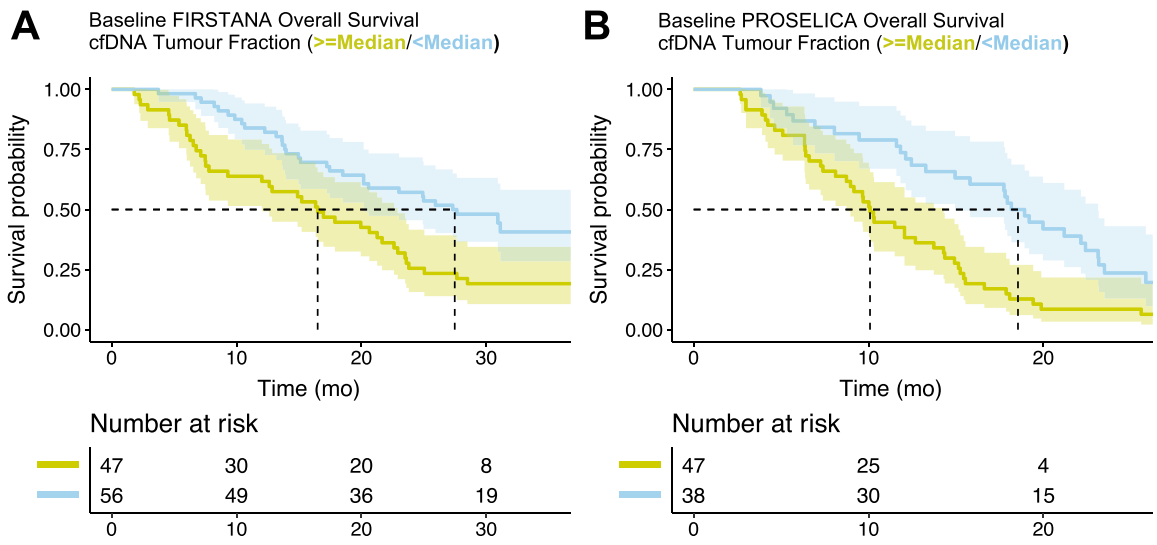
[b] Stratification parameters.

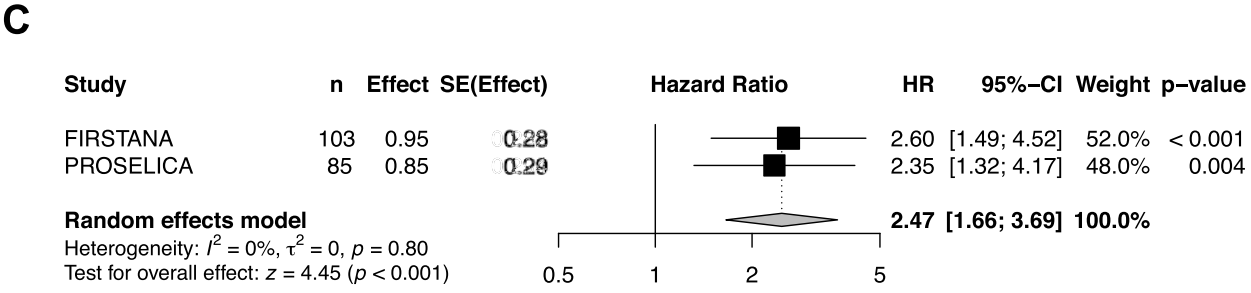
[c] Twenty assessments missing (15 in FIRSTANA and 5 in PROSELICA).

[d] Twelve assessments missing (5 in FIRSTANA and 7 in PROSELICA).

[e] Wilcoxon rank-sum test.

[f] Log-rank test.





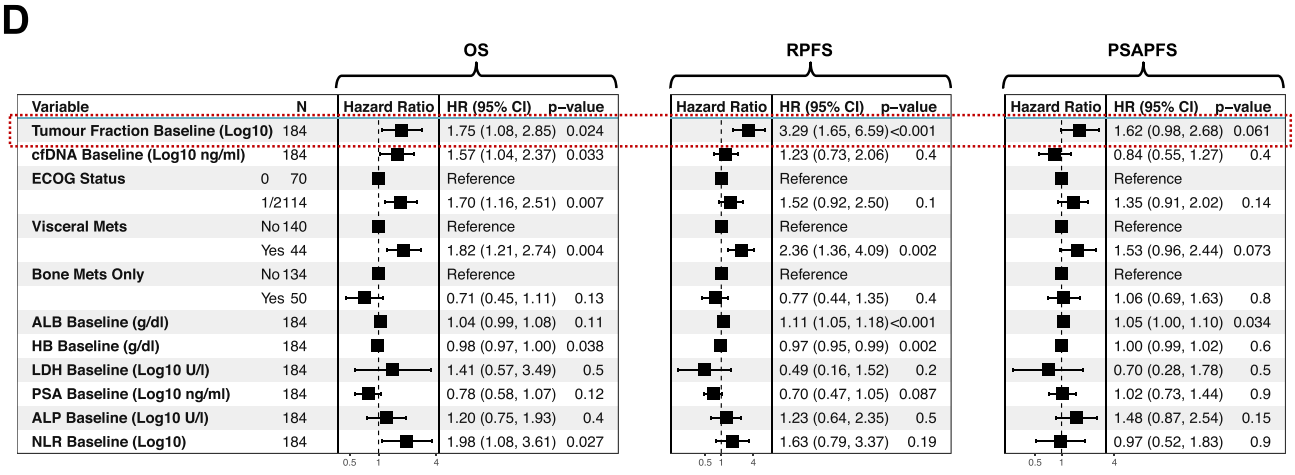


Fig. 1 – Cell-free DNA (cfDNA) tumour fraction estimates are prognostic. (A,B) Univariable analysis of overall survival (OS) with cohort stratification by median baseline tumour fraction (average for the screening and cycle 1 day 1 samples; yellow = high, blue = low) across the (A) FIRSTANA (discovery) and (B) PROSELICA (validation) cohorts. Kaplan-Meier plots with confidence intervals (CIs) and matching risk tables are shown. Dashed lines indicate the time to 50% survival. (C) Univariable regression random-effects meta-analysis of OS by cfDNA tumour fraction (continuous variable, $\log_{10}$ transformed) in the FIRSTANA (discovery) and PROSELICA (validation) cohorts. Effect size, hazard ratio (HR), 95% CI, and p values for the overall test for effect are shown. SE = standard error. (D) Forest plots showing multivariable analysis of OS, radiographic progression-free survival (RPFS) and PSA progression-free survival (PSAPFS) from Cox proportional-hazards models. Statistical models were stratified by study inclusion (FIRSTANA vs PROSELICA) because of underlying differences in survival. The median baseline tumour fraction (continuous variable, $\log_{10}$-transformed) and median baseline cfDNA total concentration (continuous variable, log10-transformed) are included in the model, along with other baseline clinical variables prognostic for mCRPC.

ECOG = Eastern Cooperative Oncology Group; Mets = metastases; ALB = albumin; HB = haemoglobin; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; ALP = alkaline phosphatase; NLR = neutrophil/lymphocyte ratio.

characteristics for the 188 patients involved are presented in Table 1 (FIRSTANA $n = 103$ and PROSELICA $n = 85$; Supplementary Figs. 1 and 2). PROSELICA substudy patients had worse prognostic characteristics than the FIRSTANA group, in keeping with a more heavily pretreated cohort. Only <2% FIRSTANA substudy patients received abiraterone/enzalutamide, in contrast to 34% of PROSELICA substudy patients. The PSA response rate was lower in PROSELICA than in FIRSTANA (39% vs 66%), similar to previous reports [5,13,14]. The baseline clinical and survival characteristics of these cohorts compared to the overall trial populations are described in Supplementary

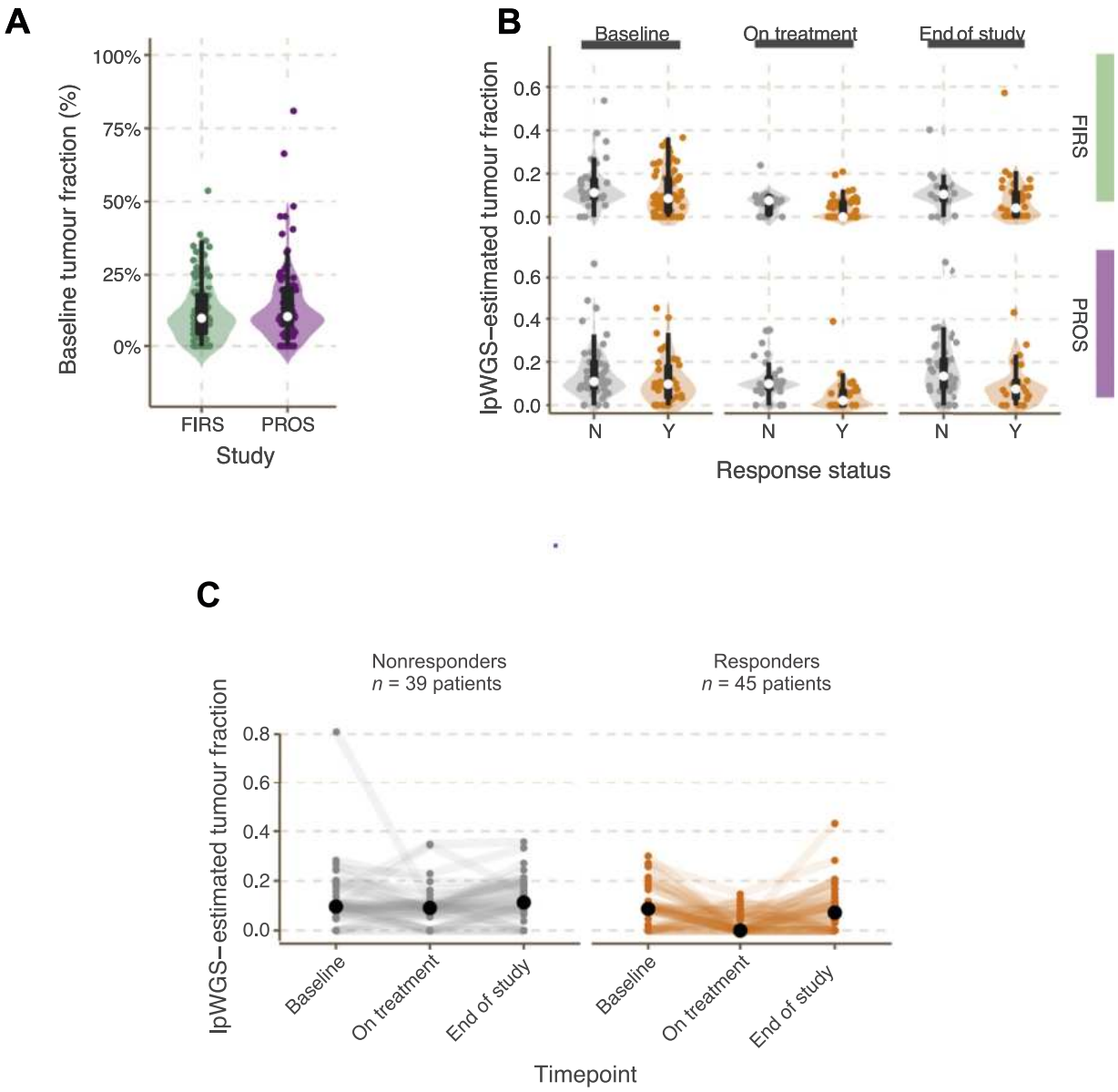


Fig. 2 – Treatment-induced changes in the tumour fraction in cell-free DNA (cfDNA). (A) Violin plots comparing baseline tumour fraction between FIRSTANA (FIRS) and PROSELICA (PROS) plasma samples. Wilcoxon rank-sum test: $p = 0.2$. Values for the median (white point; FIRS = 0.0949, PROS = 0.101), interquartile range (IQR, black rectangle; FIRS = 0.0436 to 0.175, PROS = 0.0740 to 0.197), and 1.5 × IQR (black lines) tumour fractions are also shown. (B) Violin plots illustrating changes in tumour fraction in the unmatched cohort for patients categorised as responders (either prostate-specific antigen decrease of 50% or radiographic response) or nonresponders at multiple time points. Plots are split between FIRS and PROS cohorts. Unpaired Wilcoxon rank-sum tests yielded the following results: baseline (BL) FIRS: responder ($n = 70$, median 0.0850) versus nonresponder ($n = 33$, median 0.112), $p = 0.045$; on treatment (OT) FIRS: responder ($n = 55$, median 0) versus nonresponder ($n = 22$, median 0.0755), $p = 0.003$; end of study (EOS) FIRS: responder ($n = 39$, median 0.0365) versus nonresponder ($n = 18$, median 0.105), $p = 0.035$; BL PROS: responder ($n = 34$, median 0.0976) versus nonresponder (n = 51, median 0.109), $p = 0.13$; OT PROS: responder (n = 26, median 0.0213) versus nonresponder ($n = 32$, median 0.0991), $p < 0.001$; EOS PROS: responder ($n = 22$, median 0.0766) versus nonresponder ($n = 41$, median 0.134), $p = 0.035$. (C) Analysis of matched same-patient cfDNA sample sets showing longitudinal tumour fraction changes for nonresponders ($n = 39$) and responders ($n = 45$). Median values are in black. Lines connecting points indicate same-patient sets. Paired Wilcoxon signed-rank tests yielded the following results: nonresponder BL (median 0.0966) versus OT (median 0.091), $p = 0.06$); nonresponder BL (median 0.0966) versus EOS (median 0.113), $p = 0.17$; nonresponder OT (median 0.0912) versus EOS (median 0.113), $p = 0.006$; responder BL (median 0.0873) versus OT (median 0), $p < 0.001$; responder BL (median 0.0873) versus EOS (median 0.0718), $p = 0.2$; responder OT (median 0) versus EOS (median 0.0718), $p = 0.001$.

Table 1. Maximum follow-up across the two trials was 51 and 48 mo. No differences in response or survival were noted in the substudy cohorts compared to the overall populations.

3.2. Validation of lpWGS CNA profile acquisition

lpWGS data were generated from cfDNA samples, with median sequencing coverage of 1.9X . We identified mCRPC genomic profiles (Supplementary Fig. 3) with common events including AR (chromosome Xq) and MYC (chromosome 8q) loci (Supplementary Fig. 3A). Cases with frequent large-scale CN changes described in tumours with *BRCA1/2* loss were observed [22] (Supplementary Fig. 3B), as well as focal tandem duplication patterns linked to *CDK12* loss [10] (Supplementary Fig. 3C). The overall CNA profile of our cohort was consistent with previously published mCRPC biopsy data [23] (Supplementary Fig. 3D).

To evaluate lpWGS CNA sensitivity, we used a baseline sample with an estimated tumour fraction of 50% and serially diluted it with pooled healthy volunteer cfDNA. The diluted profiles closely matched each other, but estimation of absolute CNA values was challenging when the tumour fraction was <5% (Supplementary Fig. 4A) [19]. cfDNA tumour fractions estimated via lpWGS were consistent with the expected fractions following dilution (Pearson's r = 0.994; Supplementary Fig. 4B). We further studied technical and biological replicates; ten samples subjected to duplicate library preparations showed highly correlated CNA profiles (Pearson's r = 0.948; Supplementary Fig. 4C). Biological replicates (same-patient samples taken 1–4 wk apart at SCR and C1, n = 88) showed reproducible CNAs (Supplementary Fig. 5A) and tumour fractions (Supplementary Fig. 5B).

3.3. Baseline cfDNA tumour fraction and prognosis

To explore univariable associations, we split the entire FIRSTANA + PROSELICA lpWGS cohort according to the overall median baseline ctDNA fraction, which was 9.6% (Fig. 1A). High baseline ctDNA fraction was correlated with shorter OS in the FIRSTANA and PROSELICA trials, with 10-mo-shorter median OS (Fig. 1A,B). Analysis of the tumour fraction as a continuous variable in FIRSTANA and PROSELICA independently and collectively confirmed these findings (Cox proportional-hazard models, $p < 0.001$ and p = 0.004; meta-analysis test for overall effect, $p < 0.001$; Fig. 1C). The baseline ctDNA fraction was also significantly associated with rPFS and PSA-PFS (Supplementary Fig. 6). The relationship between detectable ctDNA fraction (present/absent) on treatment and OS is shown in Supplementary Figure 7. Furthermore, the baseline ctDNA fraction was associated with several other clinical variables (Supplementary Fig. 8).

We applied a multivariable Cox proportional-hazards model, as described in the Supplementary material, to investigate OS, rPFS, and PSA-PFS (n = 184 of 188 patients with complete data) and, importantly, stratified by study inclusion (Fig. 1D) [5]. The baseline ctDNA fraction was independently associated with worse outcomes for all three endpoints; the hazard ratio was 1.75 (95% confidence interval [CI] 1.08–2.85; p = 0.024) for OS, 3.29 (95% CI 1.65–6.59; $p < 0.001$) for rPFS, and 1.62 (95% CI 0.98–2.68; p = 0.061) for PSA-PFS. We found that inclusion of the tumour fraction in multivariable survival models led to a significant improvement (OS, C index 0.722 vs 0.709; likelihood-ratio test, p = 0.021; Supplementary Table 2). These data indicate that the ctDNA fraction provides independent information in the context of established clinical biomarkers.

3.4. ctDNA fraction and response to taxane treatment

There was no statistically significant difference in baseline ctDNA fraction between the FIRSTANA and PROSELICA cohorts (median 9.5% vs 10%; Wilcoxon rank-sum test, p = 0.2; Fig. 2A). The ctDNA fraction among nonresponding FIRSTANA patients (determined via serial radiological and PSA analyses) was relatively stable throughout treatment (median 11% at baseline, 7.5% on treatment, and 10% at EOS). By contrast, the ctDNA fraction among responders exhibited large decreases on treatment (median 8.5% at baseline, 0% on treatment, and 3.7% at EOS). These observations were replicated in the PROSELICA cohort (Fig. 2B). In keeping with these findings, CNAs became undetectable in responders while on treatment (Supplementary Fig. 9). We further evaluated the ctDNA fraction in longitudinal same-patient samples (n = 252 samples from 84 patients; Fig. 2C). Among responders, the ctDNA fraction significantly decreased on treatment (Wilcoxon signed-rank test, $p < 0.001$) and increased at EOS (median 8.7% at baseline, 0% on treatment, and 7.2% at EOS); this was not observed for nonresponders (median 9.7% at baseline, 9.1% on treatment, and 11.3% at EOS).

3.5. lpWGS provides insights into PC genomic instability

We next explored LST as a measure of genomic instability [22]. PROSELICA baseline samples exhibited a significantly higher LST score compared with FIRSTANA baseline samples (Wilcoxon rank-sum test, p = 0.029; Fig. 3A); however, there was no correlation between LST score and estimated tumour fraction (Supplementary Fig. 10A). We hypothesised that LST score differences could be explained by prior treatment, and found that patients who had received abiraterone or enzalutamide had significantly higher LST scores (median LST score: 18 untreated vs 26 treated; Wilcoxon rank-sum test, p = 0.003; Fig. 3B and Supplementary Fig. 10B). Examples of CN profiles of samples with high, intermediate, and low LST scores are shown in Supplementary Figure 10C.

This was maintained in multivariable logistic regression analysis that included other known prognostic factors (including ctDNA tumour fraction) with the LST score (odds ratio 17.2, 95% CI 1.98–223; p = 0.018; Fig. 3C). However, there was no significant difference in LST score between individuals pretreated with radical radiotherapy and

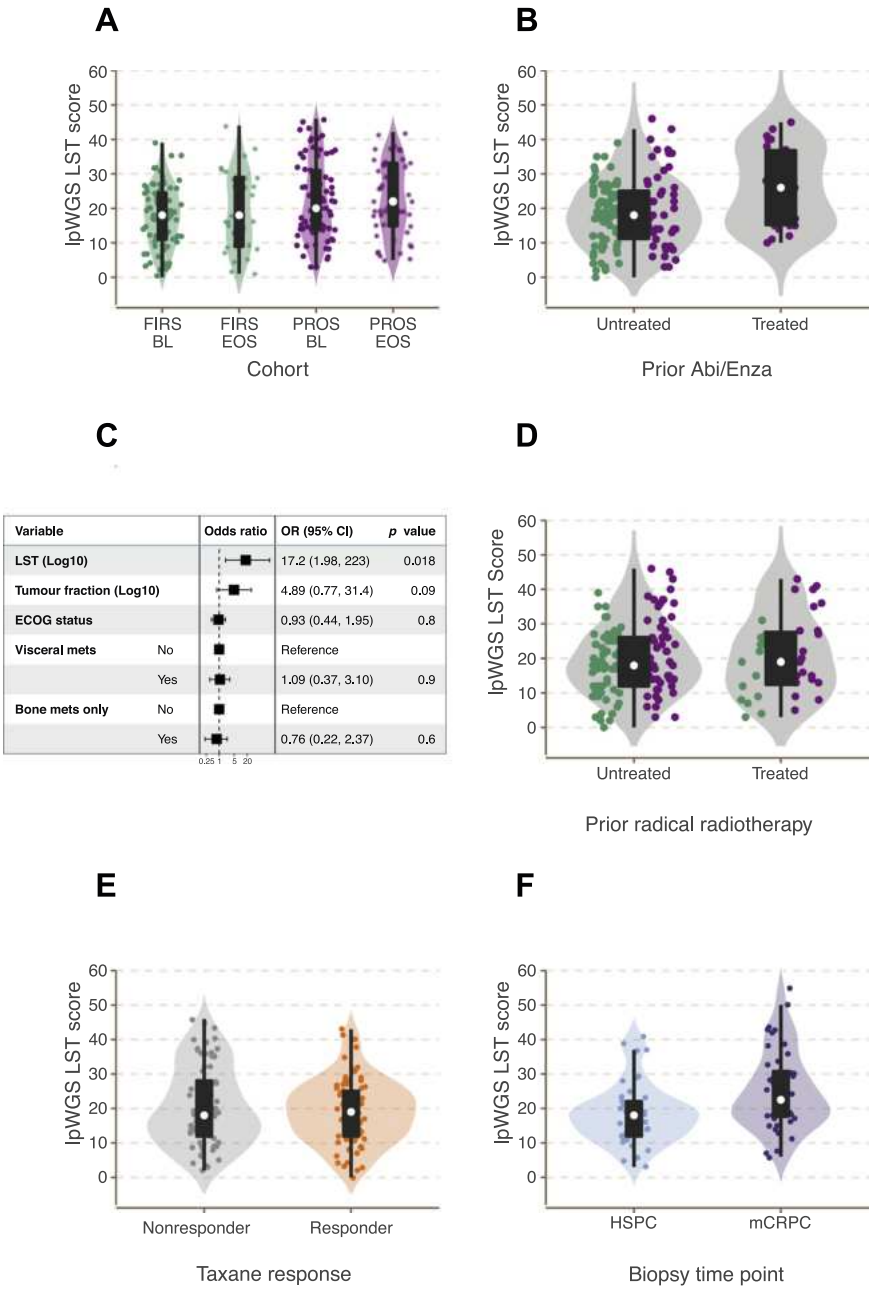
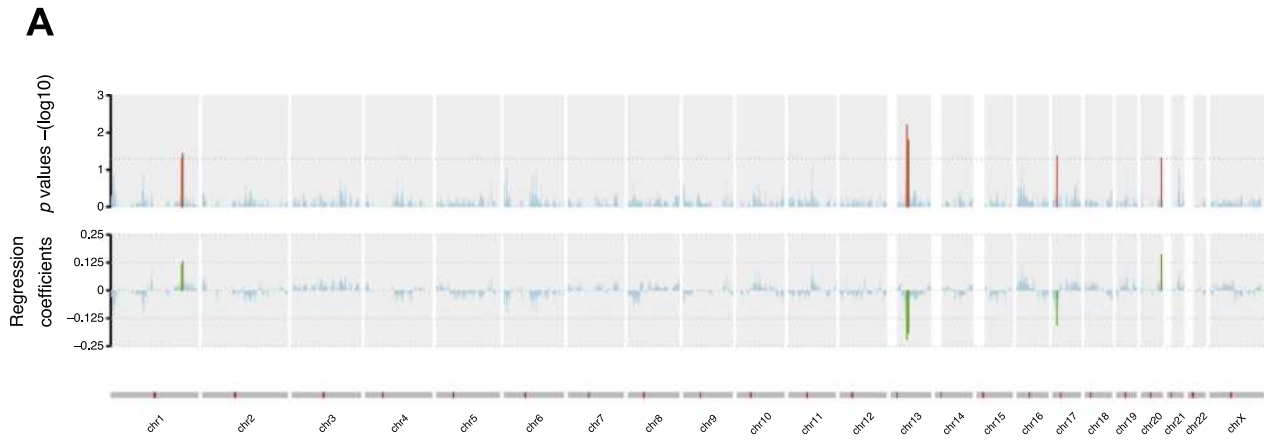


Fig. 3 – Genomic copy number burden and large-scale transition (LST) in metastatic castration-resistant prostate cancer (mCRPC). (A) Violin plot comparison of LST scores between baseline (BL) and end of study (EOS) for the FIRSTANA (FIRS) and PROSELICA (PROS) cohorts. Samples with a tumour fraction >5% were assessed; in cases with multiple BL data, the highest-fraction sample was used. Values for the median (white point), interquartile range (IQR; black rectangle) and 1.5 × IQR (black lines) LST scores are also shown. Unpaired Wilcoxon rank-sum tests yielded the following results: FIRS BL (median 18, IQR 11-24.5) versus FIRS EOS (median 18, IQR 9-29), $p = 0.5$; FIRS BL (median 18, IQR 11-24.5) versus PROS BL (median 20, IQR 14-31), $p = 0.029$; PROS BL (median 20, IQR 14-31) versus PROS EOS (median 22, IQR 15-33), $p = 0.7$. (B) Comparison of baseline LST scores between patients with prior abiraterone (Abi) or enzalutamide (Enza) exposure and untreated patients ($n = 152$). FIRSTANA patients are shown in green and PROSELICA patients in purple; after removal of cases with a low tumour fraction, no FIRSTANA patients had received Abi/Enza and a significant proportion of PROSELICA patients had received Abi/Enza. Median, IQR, and 1.5 × IQR LST scores shown as for A. Unpaired Wilcoxon rank-sum tests yielded the following results: untreated FIRS (median 18, IQR 11-24.5) versus untreated PROS (median 18, IQR 13-27.5), $p = 0.3$; overall untreated (median 18, IQR 11.2-25) versus overall treated (median 26, IQR 15.2-36.8), $p = 0.003$. (C) Forest plot of the multivariable logistic regression model for association of LST with prior Abi/Enza treatment, depicting ability of LST score to predict Abi/Enza status in the context of tumour fraction and other clinical biomarkers. (D) Comparison of baseline LST values between patients who had received prior radical radiotherapy and those who had not. FIRSTANA patients are shown in green and PROSELICA patients in purple ($n = 152$). Median, IQR, and 1.5 × IQR LST scores shown as for A. Unpaired Wilcoxon rank-sum tests yielded the following results: untreated FIRS (median 18, IQR 12-25) versus untreated PROS (median 19.5, IQR 14-31), $p = 0.10$; treated FIRS (median 17, IQR 8.25-24) versus treated PROS (median 20, IQR 14-35), $p = 0.11$; overall untreated (median 18, IQR 12-26) versus overall treated (median 19, IQR 12.5-27.5), $p = 0.8$. (E) Violin plot comparison of baseline LST scores in FIRSTANA and PROSELICA by taxane treatment response ($n = 152$). Median, IQR, and 1.5 × IQR LST scores shown as for A. A Wilcoxon rank-sum test for nonresponders (median 18, IQR 12-28) versus responders (median 19, IQR 12-25) yielded $p = 0.6$. (F) Comparison of LST scores in the validation cohort of same-patient samples (44 patients, 88 samples) between primary hormone-sensitive prostate cancer (HSPC) and mCRPC sample pairs. Median, IQR, and 1.5 × IQR LST scores shown as for A. A paired Wilcoxon rank-sum test for HSPC (median 18, IQR 12-22) versus mCRPC (median 22.5, IQR 17.8-30.8) yielded $p < 0.001$.
ECOG = Eastern Cooperative Oncology Group; Mets = metastases; OR = odds ratio; CI = confidence interval.



B

Variable		N	Estimate	Estimate (95% CI)	p value
Chr1_199.5_207.5Mb		152		3.65 (1.43, 5.86)	0.002
Chr13_44.5_52Mb		152		−7.72 (−10.3, −5.16)	<0.001
Chr17_11_15Mb		152		−4.03 (−6.01, −2.05)	<0.001
Chr20_55.5_62.5Mb		152		4.18 (2.05, 6.31)	<0.001
Prior Abi/Enza		152		1.75 (−1.99, 5.49)	0.3
Tumour Fraction (Log10)		152		4.69 (−0.20, 9.57)	0.06
Study	FIRS	79		Reference	
	PROS	73		1.15 (−1.65, 3.95)	0.4

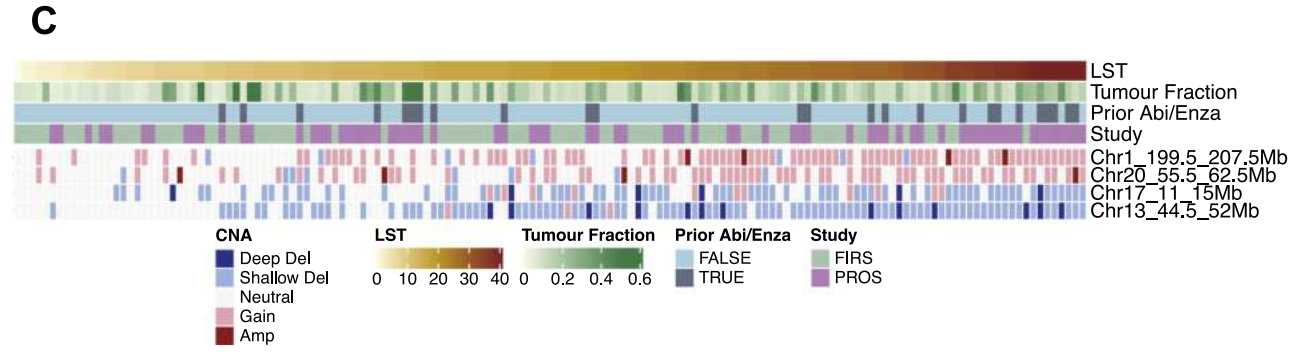


Fig. 4 – Genomic regions associated with LST. (A) Elastic-net regression model results for genome-wide copy-number alterations showing cross-validated *p* values ($-\log_{10}$-transformed) and regression coefficients for each 500-kb genomic bin. Loci with significant ($p < 0.05$) genomic alteration are depicted in red in the *p*-value plot and in green in the regression-coefficient plot. (B) Forest plot showing multivariable generalised linear model analysis of the genomic loci identified as associated with higher LST scores. Tumour fraction ($\log_{10}$-transformed), prior abiraterone (Abi) or enzalutamide (Enza) treatment, and study inclusion (FIRSTANA vs PROSELICA) were also included in the model. (C) Heatmap illustrating CNAs in regions (rows) significantly ($p < 0.05$) associated with LST scores. The samples (columns) are ordered by LST score, with additional annotation for estimated tumour fraction, prior abiraterone/enzalutamide status, and study inclusion (FIRSTANA vs PROSELICA). CNAs are coloured by type.
LST = large-scale transition; CNA = copy number alteration; Del = deletion.

untreated individuals (Fig. 3D), or between taxane responders and nonresponders (Fig. 3E).

We confirmed these findings using same-patient samples from hormone-sensitive PC (diagnostic, primary tumours) and CRPC (metastatic) biopsies (n = 88) [16], all of whom had received abiraterone or enzalutamide before CRPC biopsy (Supplementary Table 3). LST scores increased significantly (median scores 18 and 22.5; Wilcoxon rank-sum test, $p < 0.001$) after exposure to abiraterone or enzalutamide in this cohort (Fig. 3F).

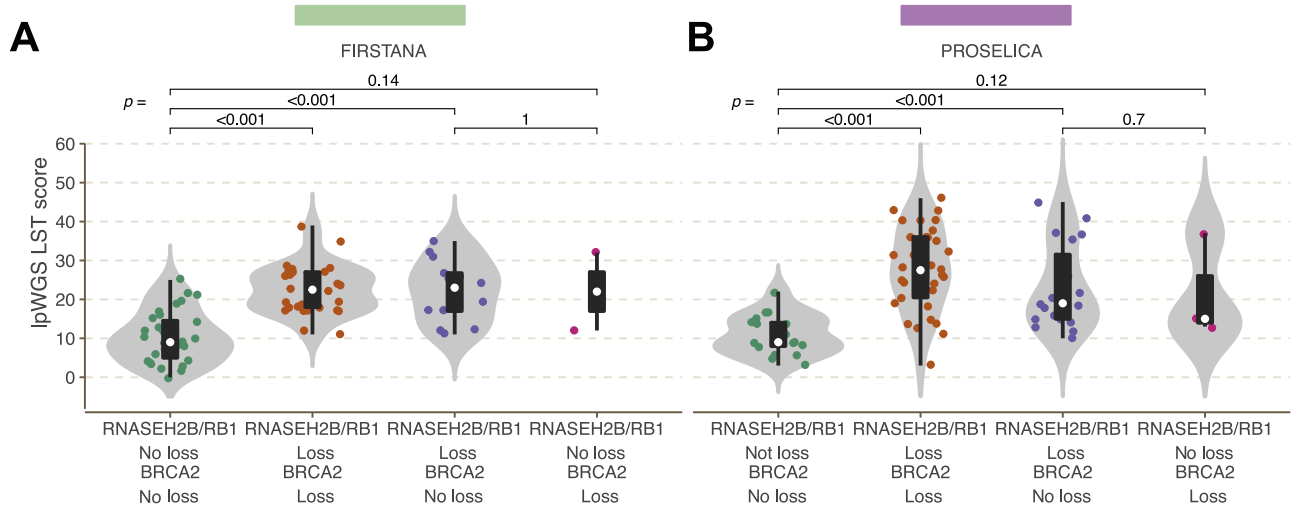


Fig. 5 – Chromosome 13 deletions and LST score. Violin plot comparisons of baseline LST scores for different chromosome 13 deletion combinations across the (A) FIRSTANA and (B) PROSELICA cohorts. Values for the median (white point), interquartile range (IQR; black rectangle), and 1.5 × IQR (black lines) LST scores are shown. The *p* values are for between-group Wilcoxon rank-sum tests.
lpWGS = low-pass whole-genome sequencing; LST = large-scale transition.

3.6. *Association of LST score with tumour CNAs*

To explore CNAs associated with LST scores, we performed elastic-net regression, which avoids false positives due to multiple testing. Among baseline samples, several CNAs were associated with high LST values ($p < 0.05$), the most significant of which was chromosome 13 loss (Fig. 4A). We then applied a multivariable generalised linear model to assess the association of these regions with LST score and found that loss of two regions on chromosomes 13 and 17, and gain of two regions on chromosomes 1 and 20 remained the most strongly associated with high LST scores (Fig. 4B).

Genes within these loci, with an overlap of publicly available PARP inhibitor CRISPR screen data, are detailed in the Supplementary material. Interestingly, when ranked by LST score, co-occurrence of several of the genomic loci most associated with a high LST score was evident (Fig. 4C). However, we surprisingly observed that the key loci highlighted by this multivariable approach did not point to *BRCA2*, but instead focused on the *RB1*/*RNASEH2B* region, although these analyses are limited by sample size and require further validation (Fig. 5A,B). Overall, these data indicate that an increase in LST score and genomic instability emerge following treatment with abiraterone or enzalutamide, but not taxane, and this is associated with *RB1* genomic locus loss with and without *BRCA2* genomic loss, with possible implication of concurrent *RNASEH2B* genomic loss.

4. Discussion

Our data show that the ctDNA fraction obtained via lpWGS provides information regarding prognosis, with serial analyses identifying responding disease. Critically, these assays provide genomic information that can serve as biomarkers of treatment response and detect genomic aberrations and signatures of DNA repair defects [10]. ctDNA lpWGS provides information on emerging mCRPC genomics and can be performed frequently, yielding data for multiple metastatic sites. However, ctDNA assays do have limitations and cannot fully elucidate intrapatient disease heterogeneity; this may be more feasible with analysis of single circulating tumour cells [24].

Interestingly, our study also shows that treatment with abiraterone or enzalutamide is associated with increases in CNAs and LST scores; this was not seen following taxane treatment or radical radiotherapy, and was maintained in the presence of other markers of tumour burden. This suggests differential, therapy-induced, genomic alterations following treatment with next-generation hormonal agents, but not taxanes. Other studies have shown that high LST scores are associated with genomic instability and may be biomarkers for PARP inhibitor sensitivity [12]. We show here that the increase in LST score following treatment with abiraterone or enzalutamide is most associated with loss of loci on chromosome 13, which usually contains the *RB1* and *RNASEH2B* genes, among others. Tumours with loss of *RNASEH2B* have been linked to impaired misincorporated RNA excision from DNA and can sensitise to PARP inhibition [25].

A limitation of ctDNA lpWGS is the fact that plasma samples containing low tumour fractions make precise detection of CNAs, especially subclonal events, challenging [19,26]. A low ctDNA fraction is nevertheless of clinical significance and indicates lower tumour burden and better outcomes. The variation in ctDNA values observed over time may reflect disease behaviour [27]. The ctDNA fraction estimated via lpWGS, unlike cfDNA concentrations [14], is highly correlated with disease response and treatment outcome, probably because a significant proportion of

cfDNA arises from nontumour sources [28,29]. Our observations support the proposal that changes in the ctDNA fraction can track treatment response, and we welcome further exploration of this phenomenon [30,31].

This study may be biased by sample selection; not all patients consented to blood sample donation for these analyses and our analyses focused on patients with available plasma with higher ctDNA levels, which may represent a poor-prognosis cohort. However, there were no statistically significant differences in the response rate or survival between our cohort and the overall trial populations. mCRPCs overall do have some of the highest quantities of cfDNA among adult solid tumour types, making these studies especially useful [32]. This study supports complementary research on ctDNA lpWGS and targeted next-generation sequencing, which together can transform disease management. Further studies to critically validate the prognostic capability of the ctDNA fraction in mCRPC are now necessary, especially in the context of existing validated biomarkers.

5. Conclusions

In conclusion, we demonstrated that cfDNA lpWGS can describe CRPC behaviour, provide prognostic and response data of clinical relevance, and identify emerging genomic alterations that might serve as therapeutic targets.

Author contributions: Johann S. de Bono 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: Sumanasuriya, Seed, Mehra, Eisenberger, Sartor, Oudard, Ozatilgan, Geffriaud-Ricouard, Chadjaa, Macé, de Bono.
Acquisition of data: Sumanasuriya, Christova, Pope, Bertan, Bianchini, Rescigno, Figueiredo, Goodall, Fowler, Flohr, Baxter, Pettitt.
Analysis and interpretation of data: Sumanasuriya, Seed, Pettit.
Drafting of the manuscript: Sumanasuriya, Seed, Rekowski, Lord, Yuan, de Bono.
Critical revision of the manuscript for important intellectual content: Sumanasuriya, Rescigno, Mehra, Neeb, Rekowski, Eisenberger, Sartor, Oudard, Ozatilgan, Geffriaud-Ricouard, Chadjaa, Macé, Lord, Lambros, Sharp, Mateo, Carreira, Yuan, de Bono.
Statistical analysis: Seed, Parr, Rekowski.
Obtaining funding: Eisenberger, Sartor, Oudard, Geffriaud-Ricouard, Chadjaa, Macé, de Bono.
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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.2021.05.030.

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Philipp Dahm[a,b,*], Juan Franco[c]
[a]Urology Section, Minneapolis Veterans Administration Medical Center, Minneapolis, MN, USA
[b]Department of Urology, University of Minnesota, Minneapolis, MN, USA
[c]Department of Family Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

*Corresponding author. Urology Section, Minneapolis VA Health Care System, One Veterans Drive, Minneapolis, MN 55417, USA.
E-mail address: pdahm@umn.edu (P. Dahm).

Re: Complications Associated with Ureteroscopic Management of Upper Tract Urothelial Carcinoma

Linehan J, Schoenberg M, Seltzer E, Thacker K, Smith AB

Urology 2021;147:87–95

Experts' summary:

The authors reviewed the complications associated with conservative management of upper tract urothelial carcinoma (UTUC). Their meta-analysis covered a long period and assessed the morbidity of retrograde and percutaneous management of low-grade UTUC. Seven prospective and 31 retrospective studies were reviewed, including nearly 1200 patients and more than 2500 procedures. Complications after endoscopic UTUC resection or laser ablation were assessed, as well as those associated with endoscopic adjuvant treatments, including mitomycin C and bacillus Calmette-Guérin (BCG).

Fatal complications were rare. After endoscopic procedures, the median rate of secondary ureteral stricture was 10% (range 0–27%), with ureteral perforation, bleeding, and fever/urinary tract infection (UTI) observed in 1.3–7.4%, 1.6–8.1%, and 2.7–11.1% of the patients, respectively. Other complications were rarely described, even anecdotally.

Adjuvant instillations of mitomycin or BCG, administered via a JJ stent or percutaneous nephrostomy, were responsible for various complications, including infection, fever, bleeding, and lower urinary tract symptoms, in up to 90% of patients.

Experts' comments:

Current recommendations suggest conservative management for low-risk UTUC, namely unifocal tumors of <2 cm in size and low grade on cytology and biopsy, in the absence of invasion on computed tomography [1,2]. Endoscopic treatment of UTUC is most frequently performed with a semirigid or flexible ureteroscope, and consists of tumor biopsy followed by tumor vaporization or resection [1,2]. A second-look examination is recommended 3 mo later [1,2]. Adjuvant intrarenal instillations of BCG or mitomycin C have been proposed, but their efficacy was not demonstrated and many complications were described [3,4]. A recent phase 3 study assessing retrograde instillations of mitomycin C in the upper urinary tract had high rates of complications including ureteral strictures (44%), UTI (23%), hematuria (31%), and pain (30%) [4]. No deaths occurred. The complication rate and the low efficacy of endoscopic instillations represent a poor benefit-risk balance for patients, and consequently new drugs and regimens are required [3].

Discounting adjuvant instillations, the complication rate after retrograde management of UTUC is acceptable and the most frequent adverse event is ureteral stricture. The risk of stricture is likely to be higher for the treatment of ureteral tumors than for pelvicaliceal tumors, and repeated procedures increase the risk. Nevertheless, endoscopic treatment of such strictures seems to be frequently successful after having differentiated stricture from UTUC recurrence [5].

Conflicts of interest: The authors have nothing to disclose.

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Alexandra Masson-Lecomte, Paul Meria*
Department of Urology, Hôpital Saint Louis, Paris, France

*Corresponding author. Department of Urology, Hôpital Saint Louis, 1 avenue Claude Vellefaux, Paris 75475, France.
E-mail address: paul.meria@aphp.fr (P. Meria).

Re: PIEZO2 in Sensory Neurons and Urothelial Cells Coordinate Urination

Marshall KL, Saade D, Ghitani N, et al

Nature 2020;588:290–5

Experts' summary:

Marshall et al [1] report that humans lacking the mechanosensitive PIEZO2 channel exhibit only one or two voids per day but frequently suffer from urinary urgency. They demonstrate that PIEZO2 is expressed in most murine bladder-innervating neurons and urothelial umbrella cells. Knockout of PIEZO2 reduced neuronal activation in response to low-threshold bladder stretching. PIEZO2 knockout mice exhibited longer intervals between voiding contractions and had enlarged bladders. According to cell type–specific knockout approaches, sensory neurons and umbrella cells contribute to this phenotype in distinct ways.

investigated ipilimumab + nivolumab (IPI-NIVO) and was the first study to report a CR rate of 10.7% and a HR for DoR of 0.48 (95% CI 0.34–0.67; $p < 0.0001$) [2]. The overall ORR for IPI-NIVO was 39.1% (95% CI 35.0–43.3), but progressive disease (PD) in 18.2% of cases indicated that IPI-NIVO did not reduce the risk of primary progression [2].

It was thought that a combination of CPI and a tyrosine kinase inhibitor (TKI) would broaden the antitumor activity and reduce the risk of primary progression. Data for axitinib + pembrolizumab (KN426) and avelumab (JR101) supported that notion, with ORR of 59.3% and 51.4%, respectively [3,4]. The proportions of patients with primary progression were numerically lower (10.9% and 11.5%, respectively), but the results did not indicate a dramatic improvement.

In CM9ER, the choice of cabozantinib as the combination partner for nivolumab contributed to its clinical efficacy. While ORR remained within the same magnitude as for AXI-based combinations, primary PD was remarkably low (5.6%) and the CR rate was promising (8.0%). This observation is in line with recent data from the CLEAR study, which tested lenvatinib in combination with pembrolizumab and reported primary PD in 5.4% of cases [5].

Is CABO-NIVO ready for prime time? In our opinion, CABO and lenvatinib set a new benchmark for efficacy in combinations and represent a novel SOC. Broad clinical activity and a lower risk of primary treatment failure are benefits associated with these combinations. This is clearly advantageous in comparison to other combinations and to IPI-NIVO in particular. However, long-term survival and DoR remain strengths of IPI-NIVO and additional follow-up of CM9ER is needed to reveal the full benefit of this combination.

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Re: Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Powles T, Rosenberg JE, Sonpavde GP, et al

N Engl J Med 2021;384:1125–35

Experts' summary:

EV-301, a phase 3 trial of 608 patients with locally advanced or metastatic urothelial carcinoma (UC) previously treated with immune checkpoint inhibition (ICI) and platinum-based chemotherapy, evaluated enfortumab-vedotin (EV), an antibody-drug conjugate (ADC) that targets nectin-4 and delivers monomethyl auristatin E (MMAE, a disruptor of microtubule formation) to cells expressing this protein [1].

EV exhibited superiority compared to investigator-chosen chemotherapy (docetaxel, paclitaxel, or vinflunine) for the primary endpoint of overall survival (OS; hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.56–0.80). Median OS was 12.88 mo (95% CI 8.05–10.74) with EV versus 8.97 mo (95% CI 8.05–10.74) with chemotherapy. Median progression-free survival (PFS) was 5.55 mo (95% CI 5.32–5.82) with EV versus 3.71 mo (95% CI 3.52–3.94) with chemotherapy (HR 0.62, 95% CI 0.51–0.75; $p < 0.001$). The confirmed overall response was higher with EV (40.6%) than with chemotherapy (17.9%; $p < 0.001$). The median duration of response to EV was 7.39 mo. Treatment-related adverse events of grade $\geq$3 occurred in 51.4% of the EV group and 49.8% of the chemotherapy group. The most frequent adverse events for EV were maculopapular rash (7.4%), fatigue (6.4%), and a decrease in neutrophil count (6.1%), with skin reactions, peripheral neuropathy, and hyperglycemia as adverse events of special interest.

Experts' comments:

The results observed with EV are particularly noteworthy in term of the following aspects. This is the first time an ADC has shown superiority over chemotherapy in third-line treatment in a phase 3 trial in UC. EV adds another class of agents to the existing therapeutic landscape in UC. Second, EV is now a therapeutic option after platinum-containing chemotherapy and ICI, a therapeutic space that could not be filled sufficiently before. The positive data reported in terms of OS, PFS, and response rate in the third-line setting are remarkable, especially in the context of a heavily pretreated patient population and the high number of patients with negative prognostic factors (eg, liver metastases). These positive aspects are accompanied by a tolerable safety profile. The key-lock mechanism targeting nectin-4 as a cellular receptor allows the delivery of high intracellular concentrations of MMAE as the therapeutic agent into

cancer cells [2]. The high expression of nectin-4, particularly in UC cells, helps to reduce off-target effects and thereby minimize unwanted systemic adverse effects to a large extent. Existing data have already demonstrated the potential of EV as a game changer in the treatment of advanced UC [3]. Of particular interest now is whether the potential of EV is confirmed in earlier treatment lines, as explored in the Keynote 915 trial evaluating EV in combination with pembrolizumab in the perioperative setting for muscle-invasive bladder carcinoma [4]. The same combination of EV plus ICI is also being investigated in the EV302 trial in the first-line setting [5]. Therefore, EV as a first-in-class agent represents a significant enrichment of the therapeutic landscape for UC, with its full potential still emerging.

Conflicts of interest: Jens Bedke has received personal fees for speaker, consultancy, or advisory roles from AstraZeneca, Astellas, BMS, Eisai, Ipsen, MSD, Novartis, Roche, EUSA Pharma, and Pfizer, and institutional fees from Astellas, Eisai, Ipsen, MSD, Novartis, Roche, Seattle Genetics, and Pfizer. Moritz Maas has nothing to disclose.

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Jens Bedke*, Moritz Maas
Department of Urology, Eberhard Karls University, Tübingen, Germany

*Corresponding author. Department of Urology, Eberhard Karls University, Hoppe-Seyler Straße 3, 72076 Tübingen, Germany.
E-mail address: jens.bedke@med.uni-tuebingen.de (J. Bedke).

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Re: Evaluation of Patient- and Surgeon-specific Variations in Patient-reported Urinary Outcomes 3 Months After Radical Prostatectomy from a Statewide Improvement Collaborative

Auffenberg GB, Qi J, Dunn RL, et al

JAMA Surg 2021;156:e206359

Experts' summary:

Between April 2014 and July 2018, 4582 men scheduled to undergo radical prostatectomy (RP) as primary treatment for localized prostate cancer (PCa) were invited to complete validated functional questionnaires before surgery and at 3, 6, and 12 mo after surgery [1]. The aim of this prospective population-based cohort study was to clarify which patient-specific factors are associated with urinary outcomes 3 mo after surgery. In addition, the authors determined the percentage of a surgeon's patients who reported good urinary function at baseline and at 3 mo to define surgeon-specific variation in both urinary function and two measures of cancer control (postoperative prostate-specific antigen $<$0.1 ng/ml and negative surgical margins in cases of organ-confined disease).

Older age, body mass index $\geq$30 kg/m^2, and clinical stage $\geq$T2a were associated with worse 3-mo urinary outcomes. Moreover, patients with higher baseline urinary function and who received bilateral nerve-sparing surgery were more likely to report good function.

Across the 48 surgeons included in the surgeon-level analyses, the percentage of patients who reported good urinary function at baseline and 3 mo varied from 0% to 54.5%. On the basis of these results, 12 surgeons were classified as the top-performing surgeons.

Regardless of patient-specific factors, the patients who were operated on by the top-performing surgeons consistently reported better functional and oncological outcomes. Strikingly, annualized prostatectomy volume did not differ for top-performing surgeons (median of 28 cases per year) and those in the lowest-performing quartile (median of 17 cases per year).

Experts' comments:

RP is a complex procedure owing to the unique anatomical location of the prostate gland, which clearly impacts both cancer control and functional objectives. The learning curve for RP has previously been defined. Remarkably, significant reductions in oncological outcomes are not observed before more than 200, 350, and 100 cases of open RP (ORP), laparoscopic RP (LRP), and robotic RP (RARP), respectively [2,3]. In terms of functional outcomes, more than 100 cases are needed before the surgical learning curve reaches a plateau for urinary continence recovery [4].

Beyond oncological outcomes, it is well known that continence is of utmost importance for patient quality of life. Therefore, novel techniques and approaches intended to preserve and maintain continence, such as Bocciardi's Retzius-sparing and Tewari's hood techniques [5], should be explored and eventually incorporated into surgical practice to improve outcomes for patients. However, the results are linked to several variables and we do not believe that it is just a matter of the technique applied. Surgeons

cancer cells [2]. The high expression of nectin-4, particularly in UC cells, helps to reduce off-target effects and thereby minimize unwanted systemic adverse effects to a large extent. Existing data have already demonstrated the potential of EV as a game changer in the treatment of advanced UC [3]. Of particular interest now is whether the potential of EV is confirmed in earlier treatment lines, as explored in the Keynote 915 trial evaluating EV in combination with pembrolizumab in the perioperative setting for muscle-invasive bladder carcinoma [4]. The same combination of EV plus ICI is also being investigated in the EV302 trial in the first-line setting [5]. Therefore, EV as a first-in-class agent represents a significant enrichment of the therapeutic landscape for UC, with its full potential still emerging.

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Jens Bedke*, Moritz Maas
Department of Urology, Eberhard Karls University, Tübingen, Germany

*Corresponding author. Department of Urology, Eberhard Karls University, Hoppe-Seyler Straße 3, 72076 Tübingen, Germany.
E-mail address: jens.bedke@med.uni-tuebingen.de (J. Bedke).

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Regardless of patient-specific factors, the patients who were operated on by the top-performing surgeons consistently reported better functional and oncological outcomes. Strikingly, annualized prostatectomy volume did not differ for top-performing surgeons (median of 28 cases per year) and those in the lowest-performing quartile (median of 17 cases per year).

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Beyond oncological outcomes, it is well known that continence is of utmost importance for patient quality of life. Therefore, novel techniques and approaches intended to preserve and maintain continence, such as Bocciardi's Retzius-sparing and Tewari's hood techniques [5], should be explored and eventually incorporated into surgical practice to improve outcomes for patients. However, the results are linked to several variables and we do not believe that it is just a matter of the technique applied. Surgeons

usually modify their techniques on the basis of disease understanding and their hands-on experience in order to improve results. The relationship between case load, experience, and surgical technique represents a compelling measure in assessing performance and most importantly for actual patient reported-outcomes [6].

Although Auffenberg et al [1] did not identify significant differences in terms of surgeon annual volume, do these findings actually mean that surgeon experience does not play a significant role in obtaining favorable functional results? Probably not.

First, previous surgical experience is not reported for the surgeons in the study, and if surgical volume did not impact outcomes, this might be related to the fact that the annual RP volume is of similar magnitude for all the surgeons. Therefore, this work is limited to an investigation of the role of volume, since all surgeons had a similar case load during the 4-yr study period. Second, the analysis included 2818 RP procedures without specifying the approach (ORP or RARP), although the impact of the approach on patient outcomes might be as important as the technique used. Third, the surgeon-level analysis was performed using data for 3-mo patient-reported urinary function, even though the variation in patient scores was greatest at that time point. Perhaps an analysis at 6 or 12 mo after RP could provide a more detailed picture of the actual situation.

We must keep in mind that given the variability not only in the surgical approach (ORP, LRP, or RARP) but also in the surgical technique, identifying which techniques are performed by the surgeons who achieve better results is mandatory, as stated by Auffenberg et al [1]. That been said, we should not be tempted to conclude that surgeon experience is not decisive: as Vladimir Horowitz said, "The difference between ordinary and extraordinary is practice."

In any case, these results suggest that there is a need to: (1) identify which techniques lead to better results; (2) facilitate effective knowledge transfer to eventually shorten the learning curve, so that fewer patients suffer the effects of inexperience; and (3) recognize that evaluation of surgical performance is paramount. Of great consequence, fellowship training, proctorships and continues evaluation of outcomes should be further promoted to improve current results [7]. The bottom line is accurate training, not only at the start but throughout a surgeon's whole career, with extensive and rigorous evaluation.

As a junior surgeon, the golden opportunity to learn, practice, and simultaneously improve surgical skills under knowledgeable mentoring is essential to become a future "top-performing surgeon". It represents a natural transfer of experience. In addition, trainees should learn that appraisal of the outcomes achieved by each surgeon should be clearly disclosed to the patient and not necessarily just results published by referral centers. Patients should be aware that outcomes from both referral centers and seasoned surgeons might be better than those seen in other institutions with more limited experience.

Conflicts of interest: The authors have nothing to disclose.

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Lara Rodríguez Sánchez[a,*], Alexandre Mottrie[b,c], Markus Graefen[d], Xavier Cathelineau[e], Alberto Breda[f], Rafael Sanchez-Salas[e]
on behalf of the EAU Robotic Urology Section*Corresponding author. Department of Urology, Hospital Universitario Miguel Servet, Paseo Isabel la Católica, 1–3, 50009 Zaragoza, Spain.
[a]*Department of Urology, Hospital Universitario Miguel Servet, Zaragoza, Spain*
[b]*Department of Urology, OLV Hospital, Aalst, Belgium*
[c]*ORSI Academy, Melle, Belgium*
[d]*Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany*
[e]*Department of Urology, L'Institut Mutualiste Montsouris, Université Paris-Descartes, Paris, France*
[f]*Department of Urology, Fundació Puigvert, Universidad Autonoma de Barcelona, Barcelona, Spain*
E-mail address: lrodriguezsan@salud.aragon.es (L. Rodríguez Sánchez).

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Experts' comments:
The afferent nerves and the urothelium play important roles in the sensing of bladder distension and in translating this into signals for local and central nervous system control of bladder function [2]. It is assumed that ion channels, including members of the transient receptor potential family and stretch-dependent K^+ channels, are involved in the sensing of bladder filling [3]. Marshall et al [1] provide strong evidence that another mechanosensitive ion channel, PIEZO2, plays a major role in the sensing of bladder filling. The similar phenotype in mice and humans lacking PIEZO2 supports the translational relevance of the murine findings.

These findings are intriguing in several ways. First, they provide a mechanistic basis for the observation that urgency and frequency can be regulated differently and are correlated with each other only poorly to moderately. This challenges the policy of regulatory authorities to base approval of overactive bladder medicines primarily on incontinence and frequency, and not on urgency data. Such focus of the regulatory authorities may have contributed to limited efforts in the discovery and development of drugs primarily targeting urgency. Second, the highly restricted expression of PIEZO2 within the bladder may explain why this channel did not surface as an attractive player in studies exploring gene expression in the overall bladder. Third, the new data not only confirm the roles of sensory neurons and urothelial umbrella cells in the regulation of voiding but also highlight that each of these cell types contributes in a distinct way to the regulation of bladder function in vivo. Although details of the specific roles and their interaction remain to be established, the ability of umbrella cells to impact bladder compliance, via insertion of membrane (thus increasing their size) as the bladder is stretched upon filling, may involve PIEZO2. In addition, the increase in bladder wall remodeling that occurs in PIEZO2 knockout mice may also suggest alterations in the extracellular matrix. As the bladder fills, the extracellular matrix impacts the ability of the urothelium to sense changes in mechanical deformation occurring during a micturition cycle and, in turn, release mediators that influence sensation. Taken together, these findings reveal that PIEZO2 is involved in mechanochemical transduction in the urinary bladder. Finally, these data provide opportunities for the exploration of novel treatments for bladder dysfunction. We propose that progress in our understanding of bladder pathophysiology and the development of novel therapeutics will require focus on specific subsets of patients with distinct biomarkers and/or symptom constellations rather than looking at broad categories such as overactive bladder syndrome.

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Conflicts of interest: Martin C. Michel is a former employee of and current consultant for Boehringer Ingelheim; is a consultant for Apogepha, Astellas, Dr. Willmar Schwabe, Sanofi, and Velicept; and is a shareholder of Velicept. Lori A. Birder has nothing to disclose.

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Martin C. Michel[a,*], Lori A. Birder[b,c]
[a]*Department of Pharmacology, Johannes Gutenberg University Mainz, Mainz, Germany*
[b]*Department of Medicine, Renal Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[c]*Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

*Corresponding author. Department of Pharmacology, Johannes Gutenberg University Mainz, Mainz, Germany.
E-mail address: marmiche@uni-mainz.de (M.C. Michel).

Re: Nivolumab plus Cabozantinib Versus Sunitinib for Advanced Renal-cell Carcinoma

Choueiri TK, Powles T, Burotto M, et al

N Engl J Med 2021;384:829–41

Experts' summary:
Cabozantinib (CABO) and nivolumab (NIVO) are standard therapies for patients with previously treated metastatic renal cell carcinoma (mRCC). The combination of both (CABO-NIVO) in the CM9ER study improved progression-free survival (PFS; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.41–0.64; $p < 0.001$) and overall survival (OS; HR 0.60, 95% CI 0.40–0.89; $p = 0.001$) compared to sunitinib in the first line. A similar impact was detected for the objective response rate (ORR; 55.7% vs 27.1%; $p < 0.001$) [1]. The incidence of grade $\geq$3 toxicities was 70.6% for CABO-NIVO and 75.3% for sunitinib. These data indicate that CABO-NIVO is a candidate for a novel standard of care (SOC) in the competitive first-line setting in mRCC.

Experts' comments:
The treatment landscape in mRCC has changed rapidly in recent years. The advent of checkpoint inhibitors (CPIs) shifted our treatment expectations towards complete response (CR) and duration of response (DoR). CM214

investigated ipilimumab + nivolumab (IPI-NIVO) and was the first study to report a CR rate of 10.7% and a HR for DoR of 0.48 (95% CI 0.34–0.67; $p < 0.0001$) [2]. The overall ORR for IPI-NIVO was 39.1% (95% CI 35.0–43.3), but progressive disease (PD) in 18.2% of cases indicated that IPI-NIVO did not reduce the risk of primary progression [2].

It was thought that a combination of CPI and a tyrosine kinase inhibitor (TKI) would broaden the antitumor activity and reduce the risk of primary progression. Data for axitinib + pembrolizumab (KN426) and avelumab (JR101) supported that notion, with ORR of 59.3% and 51.4%, respectively [3,4]. The proportions of patients with primary progression were numerically lower (10.9% and 11.5%, respectively), but the results did not indicate a dramatic improvement.

In CM9ER, the choice of cabozantinib as the combination partner for nivolumab contributed to its clinical efficacy. While ORR remained within the same magnitude as for AXI-based combinations, primary PD was remarkably low (5.6%) and the CR rate was promising (8.0%). This observation is in line with recent data from the CLEAR study, which tested lenvatinib in combination with pembrolizumab and reported primary PD in 5.4% of cases [5].

Is CABO-NIVO ready for prime time? In our opinion, CABO and lenvatinib set a new benchmark for efficacy in combinations and represent a novel SOC. Broad clinical activity and a lower risk of primary treatment failure are benefits associated with these combinations. This is clearly advantageous in comparison to other combinations and to IPI-NIVO in particular. However, long-term survival and DoR remain strengths of IPI-NIVO and additional follow-up of CM9ER is needed to reveal the full benefit of this combination.

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Re: Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Powles T, Rosenberg JE, Sonpavde GP, et al

N Engl J Med 2021;384:1125–35

Experts' summary:

EV-301, a phase 3 trial of 608 patients with locally advanced or metastatic urothelial carcinoma (UC) previously treated with immune checkpoint inhibition (ICI) and platinum-based chemotherapy, evaluated enfortumab-vedotin (EV), an antibody-drug conjugate (ADC) that targets nectin-4 and delivers monomethyl auristatin E (MMAE, a disruptor of microtubule formation) to cells expressing this protein [1].

EV exhibited superiority compared to investigator-chosen chemotherapy (docetaxel, paclitaxel, or vinflunine) for the primary endpoint of overall survival (OS; hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.56–0.80). Median OS was 12.88 mo (95% CI 8.05–10.74) with EV versus 8.97 mo (95% CI 8.05–10.74) with chemotherapy. Median progression-free survival (PFS) was 5.55 mo (95% CI 5.32–5.82) with EV versus 3.71 mo (95% CI 3.52–3.94) with chemotherapy (HR 0.62, 95% CI 0.51–0.75; $p < 0.001$). The confirmed overall response was higher with EV (40.6%) than with chemotherapy (17.9%; $p < 0.001$). The median duration of response to EV was 7.39 mo. Treatment-related adverse events of grade $\geq$3 occurred in 51.4% of the EV group and 49.8% of the chemotherapy group. The most frequent adverse events for EV were maculopapular rash (7.4%), fatigue (6.4%), and a decrease in neutrophil count (6.1%), with skin reactions, peripheral neuropathy, and hyperglycemia as adverse events of special interest.

Experts' comments:

The results observed with EV are particularly noteworthy in term of the following aspects. This is the first time an ADC has shown superiority over chemotherapy in third-line treatment in a phase 3 trial in UC. EV adds another class of agents to the existing therapeutic landscape in UC. Second, EV is now a therapeutic option after platinum-containing chemotherapy and ICI, a therapeutic space that could not be filled sufficiently before. The positive data reported in terms of OS, PFS, and response rate in the third-line setting are remarkable, especially in the context of a heavily pretreated patient population and the high number of patients with negative prognostic factors (eg, liver metastases). These positive aspects are accompanied by a tolerable safety profile. The key-lock mechanism targeting nectin-4 as a cellular receptor allows the delivery of high intracellular concentrations of MMAE as the therapeutic agent into

Philipp Dahm[a,b,*], Juan Franco[c]
[a]Urology Section, Minneapolis Veterans Administration Medical Center, Minneapolis, MN, USA
[b]Department of Urology, University of Minnesota, Minneapolis, MN, USA
[c]Department of Family Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

*Corresponding author. Urology Section, Minneapolis VA Health Care System, One Veterans Drive, Minneapolis, MN 55417, USA.
E-mail address: pdahm@umn.edu (P. Dahm).

Re: Complications Associated with Ureteroscopic Management of Upper Tract Urothelial Carcinoma

Linehan J, Schoenberg M, Seltzer E, Thacker K, Smith AB

Urology 2021;147:87–95

Experts' summary:

The authors reviewed the complications associated with conservative management of upper tract urothelial carcinoma (UTUC). Their meta-analysis covered a long period and assessed the morbidity of retrograde and percutaneous management of low-grade UTUC. Seven prospective and 31 retrospective studies were reviewed, including nearly 1200 patients and more than 2500 procedures. Complications after endoscopic UTUC resection or laser ablation were assessed, as well as those associated with endoscopic adjuvant treatments, including mitomycin C and bacillus Calmette-Guérin (BCG).

Fatal complications were rare. After endoscopic procedures, the median rate of secondary ureteral stricture was 10% (range 0–27%), with ureteral perforation, bleeding, and fever/urinary tract infection (UTI) observed in 1.3–7.4%, 1.6–8.1%, and 2.7–11.1% of the patients, respectively. Other complications were rarely described, even anecdotally.

Adjuvant instillations of mitomycin or BCG, administered via a JJ stent or percutaneous nephrostomy, were responsible for various complications, including infection, fever, bleeding, and lower urinary tract symptoms, in up to 90% of patients.

Experts' comments:

Current recommendations suggest conservative management for low-risk UTUC, namely unifocal tumors of <2 cm in size and low grade on cytology and biopsy, in the absence of invasion on computed tomography [1,2]. Endoscopic treatment of UTUC is most frequently performed with a semirigid or flexible ureteroscope, and consists of tumor biopsy followed by tumor vaporization or resection [1,2]. A second-look examination is recommended 3 mo later [1,2]. Adjuvant intrarenal instillations of BCG or mitomycin C have been proposed, but their efficacy was not demonstrated and many complications were described [3,4]. A recent phase 3 study assessing retrograde instillations of mitomycin C in the upper urinary tract had high rates of complications including ureteral strictures (44%), UTI (23%), hematuria (31%), and pain (30%) [4]. No deaths occurred. The complication rate and the low efficacy of endoscopic instillations represent a poor benefit-risk balance for patients, and consequently new drugs and regimens are required [3].

Discounting adjuvant instillations, the complication rate after retrograde management of UTUC is acceptable and the most frequent adverse event is ureteral stricture. The risk of stricture is likely to be higher for the treatment of ureteral tumors than for pelvicaliceal tumors, and repeated procedures increase the risk. Nevertheless, endoscopic treatment of such strictures seems to be frequently successful after having differentiated stricture from UTUC recurrence [5].

Conflicts of interest: The authors have nothing to disclose.

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Alexandra Masson-Lecomte, Paul Meria*
Department of Urology, Hôpital Saint Louis, Paris, France

*Corresponding author. Department of Urology, Hôpital Saint Louis, 1 avenue Claude Vellefaux, Paris 75475, France.
E-mail address: paul.meria@aphp.fr (P. Meria).

Re: PIEZO2 in Sensory Neurons and Urothelial Cells Coordinate Urination

Marshall KL, Saade D, Ghitani N, et al

Nature 2020;588:290–5

Experts' summary:

Marshall et al [1] report that humans lacking the mechanosensitive PIEZO2 channel exhibit only one or two voids per day but frequently suffer from urinary urgency. They demonstrate that PIEZO2 is expressed in most murine bladder-innervating neurons and urothelial umbrella cells. Knockout of PIEZO2 reduced neuronal activation in response to low-threshold bladder stretching. PIEZO2 knockout mice exhibited longer intervals between voiding contractions and had enlarged bladders. According to cell type–specific knockout approaches, sensory neurons and umbrella cells contribute to this phenotype in distinct ways.

Experts' comments:
The afferent nerves and the urothelium play important roles in the sensing of bladder distension and in translating this into signals for local and central nervous system control of bladder function [2]. It is assumed that ion channels, including members of the transient receptor potential family and stretch-dependent K^+ channels, are involved in the sensing of bladder filling [3]. Marshall et al [1] provide strong evidence that another mechanosensitive ion channel, PIEZO2, plays a major role in the sensing of bladder filling. The similar phenotype in mice and humans lacking PIEZO2 supports the translational relevance of the murine findings.

These findings are intriguing in several ways. First, they provide a mechanistic basis for the observation that urgency and frequency can be regulated differently and are correlated with each other only poorly to moderately. This challenges the policy of regulatory authorities to base approval of overactive bladder medicines primarily on incontinence and frequency, and not on urgency data. Such focus of the regulatory authorities may have contributed to limited efforts in the discovery and development of drugs primarily targeting urgency. Second, the highly restricted expression of PIEZO2 within the bladder may explain why this channel did not surface as an attractive player in studies exploring gene expression in the overall bladder. Third, the new data not only confirm the roles of sensory neurons and urothelial umbrella cells in the regulation of voiding but also highlight that each of these cell types contributes in a distinct way to the regulation of bladder function in vivo. Although details of the specific roles and their interaction remain to be established, the ability of umbrella cells to impact bladder compliance, via insertion of membrane (thus increasing their size) as the bladder is stretched upon filling, may involve PIEZO2. In addition, the increase in bladder wall remodeling that occurs in PIEZO2 knockout mice may also suggest alterations in the extracellular matrix. As the bladder fills, the extracellular matrix impacts the ability of the urothelium to sense changes in mechanical deformation occurring during a micturition cycle and, in turn, release mediators that influence sensation. Taken together, these findings reveal that PIEZO2 is involved in mechanochemical transduction in the urinary bladder. Finally, these data provide opportunities for the exploration of novel treatments for bladder dysfunction. We propose that progress in our understanding of bladder pathophysiology and the development of novel therapeutics will require focus on specific subsets of patients with distinct biomarkers and/or symptom constellations rather than looking at broad categories such as overactive bladder syndrome.

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Martin C. Michel[a,*], Lori A. Birder[b,c]
[a]*Department of Pharmacology, Johannes Gutenberg University Mainz, Mainz, Germany*
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The treatment landscape in mRCC has changed rapidly in recent years. The advent of checkpoint inhibitors (CPIs) shifted our treatment expectations towards complete response (CR) and duration of response (DoR). CM214

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European Association of Urology

Words of Wisdom

Re: A Systematic Review of Patients' Values, Preferences, and Expectations for the Diagnosis and Treatment of Male Lower Urinary Tract Symptoms

Malde S, Umbach R, Wheeler JR, et al

Eur Urol 2021;79:796–809

Experts' summary:
The authors conducted a protocol-driven systematic review of both quantitative and qualitative studies assessing men's values and preferences with regard to the diagnosis and treatment of male lower urinary symptoms [1]. They applied the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) and GRADE Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approaches to describe the confidence that readers can have in the findings, which was mostly moderate or low. No meta-analysis of the body of evidence identified was conducted. Important findings include that men value improvement in urgency symptoms over other symptoms (moderate certainty) and that sexual side effects of surgery are most important to those with high versus low levels of baseline function (low certainty of evidence).

Experts' comments:
Many clinicians may dismiss this study as another systematic review that tells them what they already know. However, we would argue that it provides foundational data to inform evidence-based patient care and guideline recommendations, and identifies future research priorities for men with lower urinary tract symptoms. Most management decisions in this context are highly sensitive to individual patients' values and preferences, necessitating shared decision-making (SDM). Patients' values and preferences are a critical domain when it comes to moving from evidence to decisions, and therefore systematic reviews that address what these values and preferences are and how much they may differ within the target population for a guideline are of great importance [2]. The review by Malde et al emphasizes the importance of high-quality research, but the authors found few qualitative studies, which resulted in lower certainty of evidence [3]. Of note, most studies were from high-income countries and might not adequately represent patient perceptions across different cultures and socioeconomic backgrounds.

Men's preferences for lower-risk procedures and their special concern for sexual adverse events highlight the increasing importance of minimally invasive procedures that provide an alternative to transurethral resection of the prostate [4]. These findings also support the need to develop a set of core outcomes so that they can be consistently assessed in future trials; this has been accomplished successfully for other prostatic diseases [5]. Moreover, thresholds for minimally important differences can be explored for these outcomes to inform guideline developers. Finally, whereas this review provides a comprehensive outlook on patients' perspectives, it is important for the care of each individual patient to explicitly elicit their preferences in our consultations when discussing the options via SDM.

Conflicts of interest: The authors have nothing to disclose.

CRediT authorship contribution statement

Philipp Dahm: Conceptualization, Writing - original draft. **Juan Franco:** Writing - review & editing.

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Philipp Dahm[a,b,*], Juan Franco[c]
[a]Urology Section, Minneapolis Veterans Administration Medical Center, Minneapolis, MN, USA
[b]Department of Urology, University of Minnesota, Minneapolis, MN, USA
[c]Department of Family Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

*Corresponding author. Urology Section, Minneapolis VA Health Care System, One Veterans Drive, Minneapolis, MN 55417, USA.
E-mail address: pdahm@umn.edu (P. Dahm).

Re: Complications Associated with Ureteroscopic Management of Upper Tract Urothelial Carcinoma

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Alexandra Masson-Lecomte, Paul Meria*
Department of Urology, Hôpital Saint Louis, Paris, France

*Corresponding author. Department of Urology, Hôpital Saint Louis, 1 avenue Claude Vellefaux, Paris 75475, France.
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Re: PIEZO2 in Sensory Neurons and Urothelial Cells Coordinate Urination

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building name recognition. Our findings depict 2020 as a unique crisis shaping social media use. For most urology programs, it was marked by an increase in tweets and virtual recruitment efforts. COVID-19 has altered the landscape of academic urology, with Twitter spearheading an expansion that will permeate all aspects of the field.

Conflicts of interest: The authors have nothing to disclose.

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.2021.05.002.

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[a]*Case Western School of Medicine, Cleveland, OH, USA*
[b]*Department of Urology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA*
[c]*Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA*
[d]*Department of Urology and Population Health, New York University and Manhattan Veterans Affairs, New York, NY, USA*
[e]*Indian Institute of Technology, Delhi, India*
[f]*Fox Chase Cancer Center, Department of Urology, Philadelphia, PA, USA*

*Corresponding author. Department of Urology, University Hospitals of Cleveland, 11000 Euclid Avenue, Cleveland, OH 44106, USA. Tel. +1 2168443009.
E-mail address: laura.bukavina2@uhhospitals.org (L. Bukavina).

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Mapping Contemporary Biopsy Zones to Traditional Prostatic Anatomy: The Key to Understanding Relationships Between Prostate Cancer Topography, Magnetic Resonance Imaging Conspicuity, and Clinical Risk

Pranav Satish [a,b,], Benjamin Simpson [c], Alex Freeman [d], Francesco Giganti [b,e], Alex Kirkham [e], Clement Orczyk [b,f], Hayley Whitaker [b], Mark Emberton [b,f,†], Joseph M. Norris [b,f,†]*

The traditional zonal approach to prostate anatomy devised by McNeal in 1981 [1] was based on dividing the prostate into four histologically and anatomically distinct zones. Clinically, this zonal approach has proved to have utility in both benign and cancer urology, guiding diagnostic and treatment decisions. However, this simplistic zonal approach risks conveying an overly reductive representation of prostate anatomy and may be partly responsible for the paucity of data examining differences in subzonal prostate cancer risk and prognosis, compared to the relative abundance of data comparing these features between simple tumour zones [2,3]. Furthermore, classical transrectal ultrasound-guided biopsy may have contributed to the lack of detailed understanding regarding the influence of tumour zone of origin owing to well-acknowledged undersampling of the mid and anterior prostate [4].

In the PROMIS and PICTURE trials [5,6], a transperineal template mapping (TPM) biopsy technique was used as the diagnostic reference standard, in which prostate tissue was exhaustively interrogated at 5-mm intervals, providing a unique opportunity for subzonal analysis of prostate cancer topography.

The aim of our study was to map intricate biopsy information provided by modern transperineal biopsy protocols (eg, Barzell [7], Ginsburg [8]) to the traditional McNeal anatomical zones to create a bespoke tool designed to reveal important relationships between zones of tumour origin for a wealth of other potential outcomes, including tumour conspicuity on magnetic resonance imaging (MRI) and clinical risk, as derived from histopathological, genomic, and longitudinal correlates.

We used the traditional McNeal anatomical prostate zones as our ground truth, to which we mapped Barzell and

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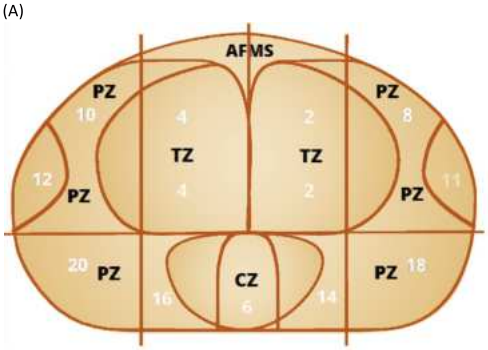

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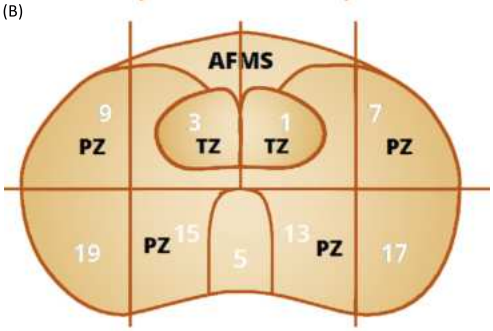

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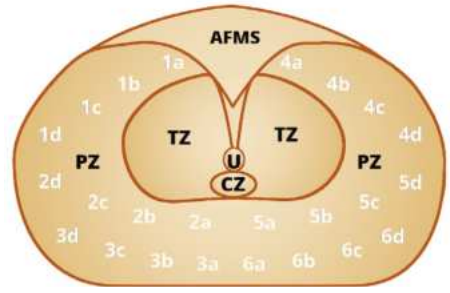

(D)

	McNeal zones	Barzell zones	Ginsburg zones
Right PZ	Anterolateral	9,10	1c, 1d
	Posterolateral	19,20	3c, 3d, 2c, 2d
	Posteromedial	15,16	3a, 3b, 2a, 2b
	Lateral	12	1d, 2d, 3d
Left PZ	Anterolateral	7,8	4c, 4d
	Posterolateral	17,18	6c, 6d, 5c, 5d
	Posteromedial	13,14	6a, 6b, 5a, 5b
	Lateral	11	4d, 5d, 6d
Urethral PZ		5,6	2a, 5a
Left TZ	Anterior	1,2	4a, 4b
	Posterior	1,2	7a, 7b
Right TZ	Anterior	3,4	1a, 1b
	Posterior	3,4	8a, 8b
CZ		6	Not definitively sampled
AFMS		Not definitively sampled	Not definitively sampled

Fig. 1 – Mapping of modern transperineal biopsy methods to the traditional McNeal zones. (A) Basal section annotated with Barzell zones. (B) Apical section annotated with Barzell zones. (C) Mid-gland annotated with Ginsburg zones. (D) Direct comparison of topographical areas of the prostate and their corresponding Barzell and Ginsburg zones. AFMS = anterior fibromuscular stroma; CZ = central zone; PZ = peripheral zone; TZ = transitional zone.

Ginsburg biopsy zones (Fig. 1). Modified Barzell zones were plotted to apical and basal sections as previously described [9], while Ginsburg zones were aligned to the mid-gland alone for simplicity.

Our proposed approach has additional factors and limitations to consider. The most important limitation is interpatient variation, particularly given the close relationship between tumour volume and age. The transitional zone (TZ) demonstrably enlarges with age due to progressive adenomatous growth in benign prostatic hyperplasia (BPH). As the TZ grows, the posterior peripheral zone (PZ) is compressed, which could conceivably alter the histopathological content of posteriorly directed prostate biopsies (eg, Barzell zones 13–20) to contain elements of both the TZ and PZ, as opposed to pure PZ sampling in men with a small- to medium-volume prostate. Indeed, these anatomical changes are also visible on MRI (eg, moustache and teardrop signs) [10]. This phenomenon may also occur in the anteromedial prostate (Barzell zones 1–4), where anterior fibromuscular stroma (AFMS) involvement may depend on the TZ size. Clinician discretion is key, and for smaller prostates it is not uncommon to limit zonal sampling, resulting in necessary recalibration of the TPM mapping protocol.

For tumours occupying multiple biopsy zones, it may be difficult to accurately ascertain the anatomical zone of origin. Nevertheless, known patterns of tumour growth may help in addressing this challenge [11]. For example, a tumour detected in Barzell zones 1 and 7 (left anterior apex) is more likely to be of TZ origin than a tumour found crossing zones 7 and 17 (anterior and posterior components of the left apex), which is likely to be exclusively of PZ origin. When uncertainty persists regarding the origin, the biopsy zone with the highest overall Gleason grade should be considered the index tumour (in accordance with the 2010 International Society of Urological Pathology consensus conference). However, if the overall Gleason grades are identical across multiple biopsy zones, then the larger foci should be considered the index tumour [12], given the plausible biological rationale that the largest tumour focus is likely to be the most mature. Lastly, it is worth recalling that PZ tumours favour horizontal over vertical extension owing to the influence of the perineural space, and the commonest location of PZ invasion by a TZ tumour is lateral to the AFMS, where the TZ-PZ stromal boundary is thinnest [13,14]. These oncological growth behaviours are useful in informing our understanding of tumour origin. However, for true determination of tumour origin, validation of this estimation with genomic analysis of the tumour foci would be necessary, especially given the theory of clonal evolution, whereby origin cells may mutate, leading to a faster growing subclone that becomes larger and of higher grade than the original tumour.

Here, we have mapped traditional zonal prostate anatomy to modern transperineal biopsy protocols to provide a pragmatic research tool that facilitates subzonal data analysis for both multiparametric MRI and histopathological outcomes. We hope that our key will provide researchers with a valuable resource for elucidating the effects of tumour location in prostate cancer diagnosis, management, and prognosis.

Conflicts of interest: Joseph M. Norris is funded by the Medical Research Council (MRC; grant MR/S00680X/1). Alex Freeman and Alex Kirkham have shares in Nuada Medical. Hayley Whitaker receives funding from Prostate Cancer UK, the Urology Foundation and Rosetrees Trust. Mark Emberton receives funding from NIHR53 i4i, MRC, Cancer Research UK, the Jon Moulton Charitable Foundation, Sonacare, Trod Medical, the Cancer Vaccine Institute, and Sophiris Biocorp for trials in prostate cancer, and acts as a consultant and/or trainer and proctor for Sonatherm, Angiodynamics, and Exact Imaging. Francesco Giganti is funded by a UCL Graduate Research Scholarship and a Brahm PhD scholarship in memory of Chris Adams. The remaining authors have nothing to disclose.

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[a]*UCL School of Medicine, University College London, London, UK*
[b]*UCL Division of Surgery & Interventional Science, University College London, London, UK*
[c]*UCL Cancer Institute, University College London, London, UK*
[d]*Department of Pathology, University College London Hospitals NHS Foundation Trust, London, UK*
[e]*Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK*
[f]*Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK*

*Corresponding author. UCL Medical School, 74 Huntley Street, Bloomsbury, London WC1E 6DE, UK.
E-mail address: pranav.satish.18@ucl.ac.uk (P. Satish).
[†]Joint senior authors.

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The European Association of Urology COVID Intermediate-priority Group is Poorly Predictive of Pathological High Risk Among Patients with Renal Tumours

Pranav Satish [a], Teele Kuusk [b], Nick Campain [b], Yasmin Abu-Ghanem [b], Joana Neves [b], Ravi Barod [b], Pranav Satish [a], Faiz Mumtaz [b], Prasad Patki [b], Maxine Tran [b], My-Anh Tran-Dang [c], Lee Grant [d], Tobias Klatte [e], Axel Bex [a,b,]*

The European Association of Urology Guidelines Office formed a Rapid Reaction Group (EAU GORRG) on March 19, 2020 [1] in response to the need for swift changes during the COVID-19 pandemic. In brief, the EAU GORRG guidelines assigned patients with suspected renal cell carcinoma (RCC) to low-, intermediate-, and high-priority groups according to their clinical TNM stage (Supplementary Table 1) [2]. Priority group allocation determined the extent to

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Research Letters

Perilesional Biopsies Increase Detection of Significant Prostate Cancer in Men with PI-RADS 4/5 Lesions: Validation of the PI-RADS Steering Committee Recommendation

John Lahoud [a], *Paul Doan* [a], *Lawrence Kim* [a,b], *Manish I. Patel* [a,b,*]

In the most recent status update by the Prostate Imaging-Reporting and Data System (PI-RADS) Steering Committee, the concept of sampling magnetic resonance imaging (MRI)-visible lesions and their "penumbra" for PI-RADS 4 and 5 lesions is recommended (Table 1 in [1]). It is important to note, however, that there is no specific definition of the "penumbra" region in this update [2]. In addition, no specific study has explored the rate of clinically significant prostate cancer (csPC) in biopsies surrounding the perimeter of the target lesion.

In our centre, in addition to transperineal targeted biopsies (TBs), biopsies were routinely taken in a ring around the perimeter of the lesion of interest, at approximately 5 mm. We describe these as perilesional biopsies (PLBs). We retrospectively reviewed 254 patients who had an abnormal prostate-specific antigen level and/or digital rectal examination and a PI-RADS score of 3–5 on multiparametric MRI who underwent transperineal TB and PLB. TB and PLB were performed using MRI-ultrasound fusion (Mona Lisa platform; Biobot Surgical, Singapore) or cognitive registration using a brachytherapy grid. A median of five TB and five PLB cores were taken, depending on the target size. Fewer cores were taken for small target lesions and lesions close to the capsule. The trajectory and tract were confirmed for both TB and PLB. Our primary outcome was to determine csPC detection rates in PLB compared to TB, using two definitions: csPC1 = International Society of Urological Pathology (ISUP) Gleason grade group (GGG) 2–5; and csPC2 = ISUP GGG 3–5. Statistical analysis was performed using Fisher's exact test with SPSS v26 (IBM Corp., Armonk, NY, USA).

Our findings show that 60/254 cases (24%) had PC identified on PLB, of which 30/254 (12%) were csPC1 and 14/254 (6%) were csPC2. When TB identified insignificant PC

		Number of patients and ISUP GGG with positive PLB						
		No cancer	1	2	3	4	5	Total
Number of patients and ISUP GGG with positive TB	No cancer	110	9	6	1	0	0	126
	1	20	12	0	2	0	0	34
	2	36	8	6	1	1	1	53
	3	13	1	2	2	0	0	18
	4	4	0	2	0	4	0	10
	5	11	0	0	0	0	2	13
	Total	194	30	16	6	5	3	254

Fig. 1 – Highest International Society of Urological Pathology (ISUP) Gleason grade group (GGG) detected via targeted biopsy (TB) in comparison to perilesional biopsy (PLB).

(iPC) or no cancer (159/254; 63%), PLB detected 9/159 cases (6%) of csPC1 ($p = 0.004$) and 3/159 (2%) of csPC2 ($p = 0.248$; Fig. 1). In 21/254 cases (8%), PLB identified PC with a higher GGG than TB ($p < 0.001$; yellow in Fig. 1).

For PI-RADS 4 and 5 lesions only, TB of the lesion revealed 90/185 cases (49%) of csPC1 and 41/185 (22%) of csPC2. When TB identified iPC or no cancer in PI-RADS 4 and 5 lesions only (95/185; 51%), PLB detected 9/95 cases (9%) of csPC1 ($p = 0.003$) and 3/95 (3%) of csPC2 ($p = 0.246$). TB of PI-RADS 4 and 5 lesions did not detect any cancer in 68/185 cases (37%), while PLB detected an extra 8/185 cases (4%) of iPC ($p = 0.481$). All cancers detected by PLB for PI-RADS 3 lesions were iPC (6/254, 2%).

Our results indicate that for PI-RADS 4 and 5 lesions, PLB in addition to TB will detect an extra 9% csPC1, at the cost of an increased 4% iPC; for PI-RADS 3 lesions, PLB biopsies do not increase the csPC detection rate. Our findings validate the recommendation of the PI-RADS Steering Committee to perform these extra biopsies of the "penumbra" region for PI-RADS 4 and 5 lesions. We propose routine PLB in addition to TB for PI-RADS 4 and 5 lesions to provide a higher likelihood of detecting csPC.

Conflicts of interest: The authors have nothing to disclose.

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[a]*Department of Urology, Westmead Hospital, Westmead, Australia*
[b]*Discipline of Surgery, Sydney Medical School, University of Sydney, Sydney, Australia*

*Corresponding author. Department of Urology, Westmead Private Hospital, Westmead, NSW 2145, Australia.
Tel. +61 2 96878252; Fax: +61 2 96870707.
E-mail address: manish.patel@sydney.edu.au (M.I. Patel).

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Growth of the Twitter Presence of Academic Urology Training Programs and Its Catalysis by the COVID-19 Pandemic

Emily Manning[a], *Adam Calaway*[b], *Justin M. Dubin*[c], *Stacy Loeb*[d], *Mohit Sindhani*[e], *Alexander Kutikov*[f], *Lee Ponsky*[b], *Kirtishri Mishra*[b], *Laura Bukavina*[b,*]

While the COVID-19 pandemic has limited face-to-face interactions, social media has proven valuable in fostering and maintaining relationships. Academic urology has embraced Twitter to enhance communication and program reputation [1–3]. With the isolating events of the pandemic, the aim of this study was to re-examine the presence of urology programs on Twitter. We hypothesized that engagement with urology residency programs would increase during 2020 compared to previous years (2009–2019).

We identified Twitter handles for 113/131 US academic urology programs listed on the American Urological Association website, and extracted 83 000 tweets from 2009–2020 through the application programming interface on April 2, 2021 using Python. Natural language processing (NLP) was used for sentiment analysis, and classified as positive, negative, or neutral. Metrics such as number of tweets, hashtags, @mentions, and account creations including timing were compared.

Figure 1 displays trends and characteristics of the academic urology programs. When assessing temporal trends, 2020 represented a significant increase in both program tweets and account creation. Compared to prior years, the number of tweets increased (from 62 in 2009 to 18 397 in 2019 and 22 544 in 2020). Furthermore, 23 urology programs created accounts in 2020, representing the single largest increase since 2009. Most programs (13/23, 57%) joined Twitter between May and June, with additional 7/23 (30%) between July and August 2020 (Supplementary material).

Sentiment analysis in 2020 revealed 43% positive, 49% neutral, and 8% negative sentiments across tweets. Interestingly, the positive sentiment percentage increased in 2020 (41% to 43%). Word cloud analysis, a visual representation of word frequency, revealed "urology" and "resident" as the most frequently utilized in 2020, compared to "urology" and "cancer" before 2020. While @americanurological remained the most frequently utilized mention in 2020, @uro_res surpassed @umichurology, as well as the recently introduced @uroresidency.

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[a]*UCL School of Medicine, University College London, London, UK*
[b]*UCL Division of Surgery & Interventional Science, University College London, London, UK*
[c]*UCL Cancer Institute, University College London, London, UK*
[d]*Department of Pathology, University College London Hospitals NHS Foundation Trust, London, UK*
[e]*Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK*
[f]*Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK*

*Corresponding author. UCL Medical School, 74 Huntley Street, Bloomsbury, London WC1E 6DE, UK.
E-mail address: pranav.satish.18@ucl.ac.uk (P. Satish).
[†]Joint senior authors.

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The European Association of Urology COVID Intermediate-priority Group is Poorly Predictive of Pathological High Risk Among Patients with Renal Tumours

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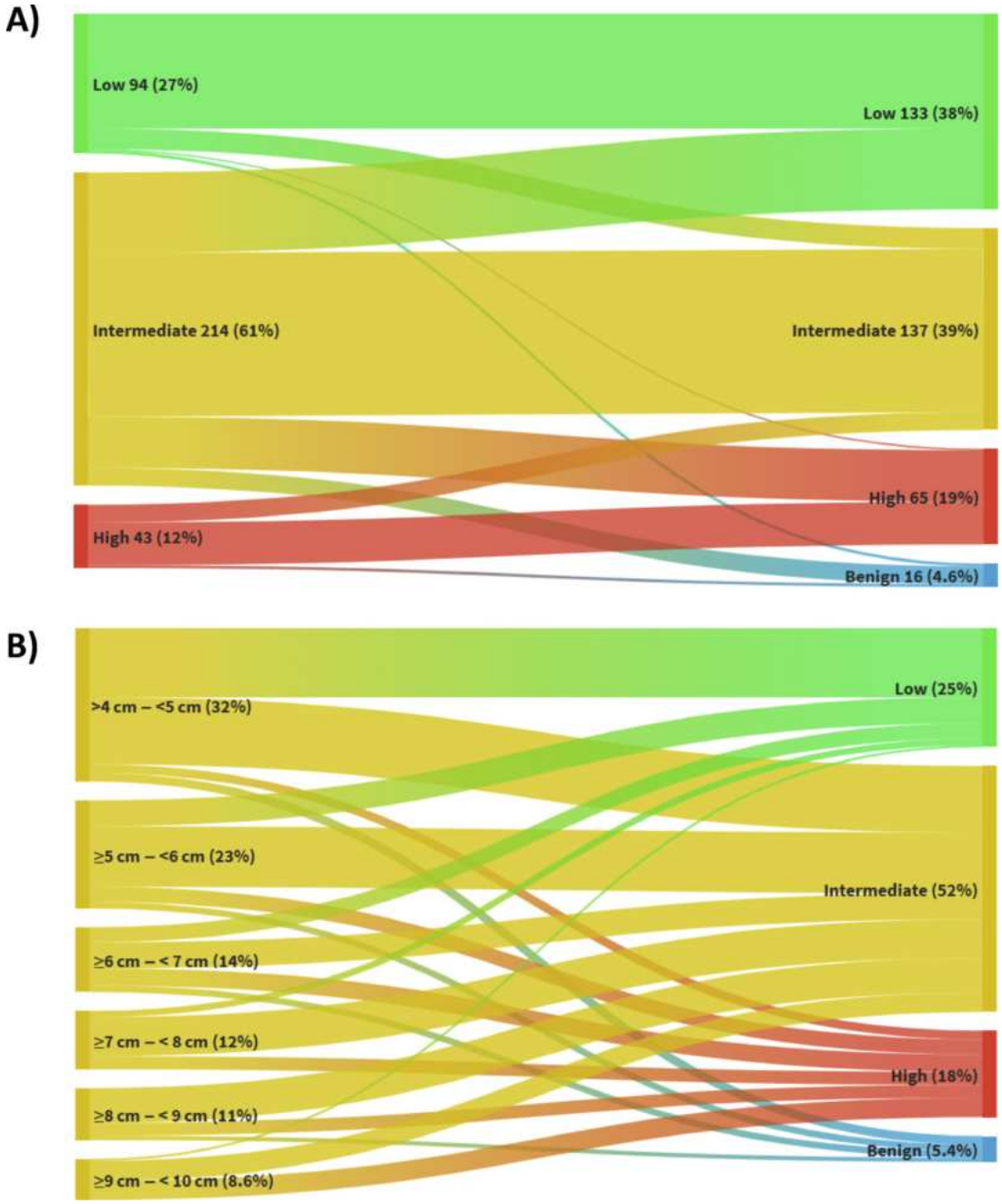

Fig. 1 – Sankey diagrams showing matching of European Association of Urology priority groups (left) to risk according to the Leibovich score (right) for patients with renal cell carcinoma. (A) Whole cohort (*n* = 351) and (B) stratification of the intermediate-priority group (*n* = 214) by 1-cm increments in tumour size.

which surgery was postponed. Despite vaccine rollout, strain on health care resources is still widespread, especially in our London centre, where national lockdown was still in place at the time of writing. Thus, the need to assess the efficacy of this system is clear, as decisions to postpone interventions must be justified by the level of clinical harm that delayed treatment could incur. To evaluate the EAU GORRG guidelines, we assessed the extent to which priority groups matched postoperative pathological risk, determined according to the 2003 Leibovich score (LS) [3].

We compared the GORRG priority groups with postoperative pathological reports for 351 patients with biopsy-proven or suspected RCC (Supplementary Table 2). LS 0–2 was considered to correspond to low GORRG priority, LS 3–5 to intermediate priority, and LS >5 to high priority. As the EAU intermediate-priority group encompasses the widest range of tumour sizes (>4 cm to ≤10 cm), we evaluated risk migration to either low or high Leibovich risk for each 1-cm increment within this group.

The least concordance between GORRG priority group and pathological risk occurred in the intermediate-priority group. A total of 102 patients (48%, 95% confidence interval [CI] 41–55%) were incorrectly prioritised, 35 of whom (16%, 95% CI 12–22%) were actually at high risk (Fig. 1). Analysis of the

intermediate-priority group by tumour size interval revealed a higher likelihood of a change to low risk for cT1b (4–7 cm) tumours than for cT2a tumours (7–10 cm; Fig. 1B). More precisely, 45% (95% CI 33–57%) of all lesions >4 cm and <5 cm would be migrated to low risk (Supplementary Table 3). In fact, our centre would have been marginally more accurate by including tumours <5 cm in the GORRG low-priority group, rather than <4 cm. Conversely, we found that among cT2a tumours (>7 cm to ≤10 cm), 32% (95% CI 22–45%) were assigned LS high risk versus only 13% (95% CI 8–19%) of cT1b tumours (>4 cm to ≤7 cm; Supplementary Table 4). With higher risk observed for 16% (95% CI 11–22%) of patients in the EAU intermediate-priority group and 16% (95% CI 10–25%) in the low-priority group, some patients may experience poorer outcomes if their treatment is deferred. Recent work by Srivastava et al [4] suggests that a delay in care of 3 mo for cT1b–cT2b tumours does not lead to greater upstaging rates or shorter overall survival. However, their study had a relatively short follow up period and only considered upstaging to pT3a in the pre-COVID era.

Overall, the system erred on the side of caution, with the GORRG guidelines overestimating risk for 67 patients (19%, 95% CI 15–24%), compared to the 50 patients (14%, 95% CI 11–18%) whose risk was underestimated. However, the cT2a intermediate-priority subgroup, in which almost one-third of the patients were upgraded to high risk, constitutes a possible exception. For future use, we therefore recommend minimising deferred interventions for intermediate-priority patients with cT2a RCC as much as possible. Conversely, at times of severely reduced resources, centres may consider intermediate-priority tumours of <5 cm as low priority.

Conflicts of interest: The authors have nothing to disclose.

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.2021.05.010.

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[a]*UCL Medical School, University College London, London, UK*
[b]*Specialist Centre For Kidney Cancer, Royal Free London NHS Foundation Trust, London, UK*
[c]*Department of Pathology, Royal Free London NHS Foundation Trust, London, UK*
[d]*Department of Radiology, Royal Free London NHS Foundation Trust, London, UK*
[e]*Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, UK*

[*]Corresponding author. Specialist Centre for Kidney Cancer, Royal Free London NHS Formation Trust, UCL Division of Surgery and Interventional Science, Pond Street, London NW3 2QG, UK.
E-mail address: a.bex@ucl.ac.uk (A. Bex).

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(iPC) or no cancer (159/254; 63%), PLB detected 9/159 cases (6%) of csPC1 ($p = 0.004$) and 3/159 (2%) of csPC2 ($p = 0.248$; Fig. 1). In 21/254 cases (8%), PLB identified PC with a higher GGG than TB ($p < 0.001$; yellow in Fig. 1).

For PI-RADS 4 and 5 lesions only, TB of the lesion revealed 90/185 cases (49%) of csPC1 and 41/185 (22%) of csPC2. When TB identified iPC or no cancer in PI-RADS 4 and 5 lesions only (95/185; 51%), PLB detected 9/95 cases (9%) of csPC1 ($p = 0.003$) and 3/95 (3%) of csPC2 ($p = 0.246$). TB of PI-RADS 4 and 5 lesions did not detect any cancer in 68/185 cases (37%), while PLB detected an extra 8/185 cases (4%) of iPC ($p = 0.481$). All cancers detected by PLB for PI-RADS 3 lesions were iPC (6/254, 2%).

Our results indicate that for PI-RADS 4 and 5 lesions, PLB in addition to TB will detect an extra 9% csPC1, at the cost of an increased 4% iPC; for PI-RADS 3 lesions, PLB biopsies do not increase the csPC detection rate. Our findings validate the recommendation of the PI-RADS Steering Committee to perform these extra biopsies of the "penumbra" region for PI-RADS 4 and 5 lesions. We propose routine PLB in addition to TB for PI-RADS 4 and 5 lesions to provide a higher likelihood of detecting csPC.

Conflicts of interest: The authors have nothing to disclose.

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[a]*Department of Urology, Westmead Hospital, Westmead, Australia*
[b]*Discipline of Surgery, Sydney Medical School, University of Sydney, Sydney, Australia*

*Corresponding author. Department of Urology, Westmead Private Hospital, Westmead, NSW 2145, Australia.
Tel. +61 2 96878252; Fax: +61 2 96870707.
E-mail address: manish.patel@sydney.edu.au (M.I. Patel).

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Growth of the Twitter Presence of Academic Urology Training Programs and Its Catalysis by the COVID-19 Pandemic

Emily Manning[a], *Adam Calaway*[b], *Justin M. Dubin*[c], *Stacy Loeb*[d], *Mohit Sindhani*[e], *Alexander Kutikov*[f], *Lee Ponsky*[b], *Kirtishri Mishra*[b], *Laura Bukavina*[b,*]

While the COVID-19 pandemic has limited face-to-face interactions, social media has proven valuable in fostering and maintaining relationships. Academic urology has embraced Twitter to enhance communication and program reputation [1–3]. With the isolating events of the pandemic, the aim of this study was to re-examine the presence of urology programs on Twitter. We hypothesized that engagement with urology residency programs would increase during 2020 compared to previous years (2009–2019).

We identified Twitter handles for 113/131 US academic urology programs listed on the American Urological Association website, and extracted 83 000 tweets from 2009–2020 through the application programming interface on April 2, 2021 using Python. Natural language processing (NLP) was used for sentiment analysis, and classified as positive, negative, or neutral. Metrics such as number of tweets, hashtags, @mentions, and account creations including timing were compared.

Figure 1 displays trends and characteristics of the academic urology programs. When assessing temporal trends, 2020 represented a significant increase in both program tweets and account creation. Compared to prior years, the number of tweets increased (from 62 in 2009 to 18 397 in 2019 and 22 544 in 2020). Furthermore, 23 urology programs created accounts in 2020, representing the single largest increase since 2009. Most programs (13/23, 57%) joined Twitter between May and June, with additional 7/23 (30%) between July and August 2020 (Supplementary material).

Sentiment analysis in 2020 revealed 43% positive, 49% neutral, and 8% negative sentiments across tweets. Interestingly, the positive sentiment percentage increased in 2020 (41% to 43%). Word cloud analysis, a visual representation of word frequency, revealed "urology" and "resident" as the most frequently utilized in 2020, compared to "urology" and "cancer" before 2020. While @americanurological remained the most frequently utilized mention in 2020, @uro_res surpassed @umichurology, as well as the recently introduced @uroresidency.

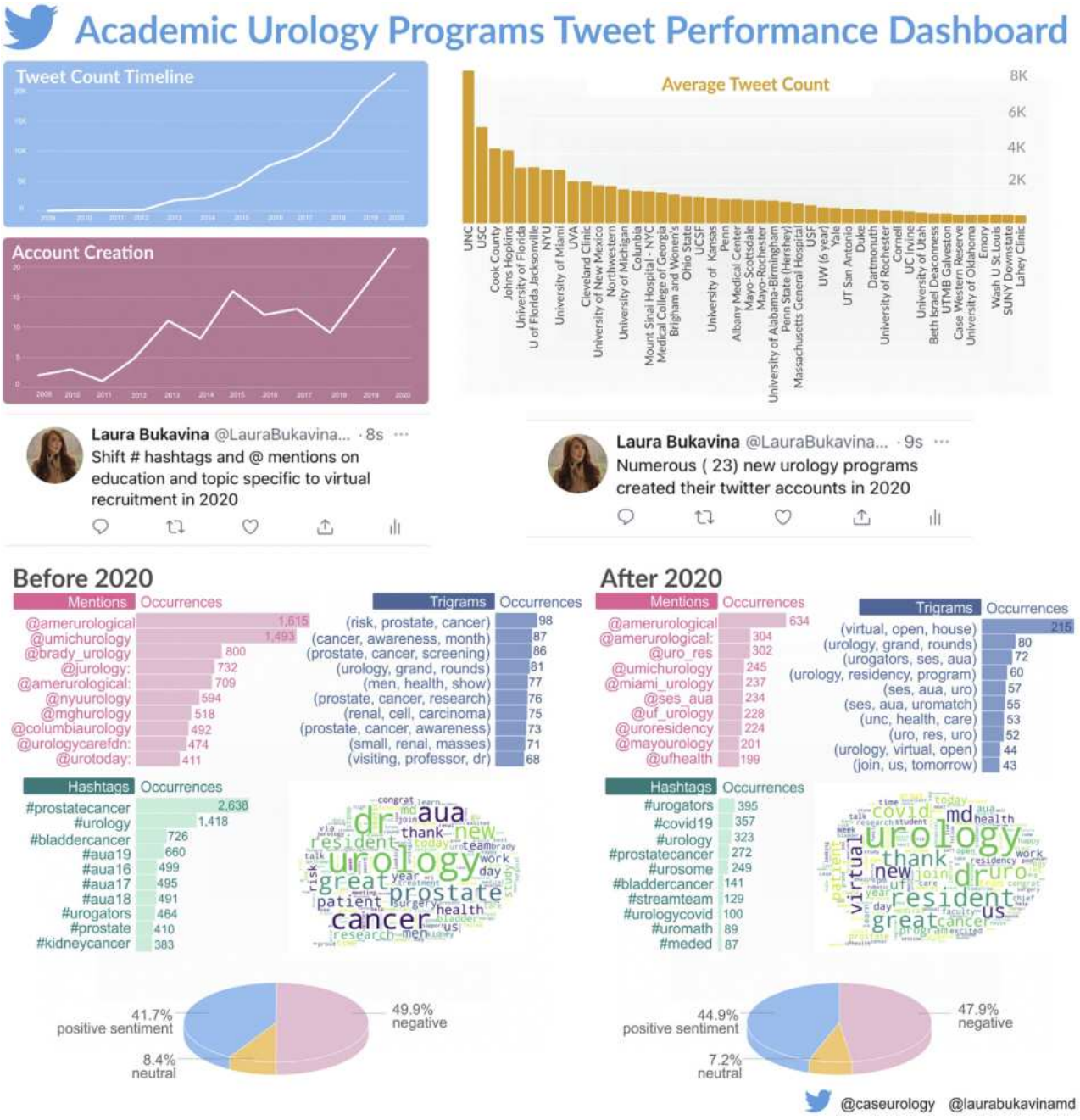

Fig. 1 – Tweet performance dashboard for academic urology programs and analysis before and after 2020.

Trigram (three-word combination) analysis for 2020 revealed a shift from a primary focus on oncology ("risk, prostate, cancer" and "cancer, awareness, month") to recruitment and education ("virtual, open, house" and "urology, grand, rounds") in 2020.

Across all programs, the median (interquartile range) number of tweets, followers, following, and likes was 1748 (872–3051), 2201 (1509–3956), 801 (307–1198), and 3 (0–3), respectively. University of North Carolina (n = 8707), University of Southern California (n = 5480), and Cook County (n = 4299) had the highest average number of tweets. Academic accounts with the most followers were Johns Hopkins (n = 5365), New York University (n = 4882), and University of Michigan (n = 4396).

Our comprehensive, novel analysis convincingly demonstrates that academic urology is expanding Twitter use in response to COVID-19. Twitter has become the academic marketing strategy, boosting conversations and distributing program-specific content globally. Twitter has allowed urology applicants to converse with program directors, residents, and educators when many classically in-person events such as away rotations and residency interviews were paused. Programs and trainees have successfully established their own personal brands,

building name recognition. Our findings depict 2020 as a unique crisis shaping social media use. For most urology programs, it was marked by an increase in tweets and virtual recruitment efforts. COVID-19 has altered the landscape of academic urology, with Twitter spearheading an expansion that will permeate all aspects of the field.

Conflicts of interest: The authors have nothing to disclose.

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.2021.05.002.

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[a]*Case Western School of Medicine, Cleveland, OH, USA*
[b]*Department of Urology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA*
[c]*Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA*
[d]*Department of Urology and Population Health, New York University and Manhattan Veterans Affairs, New York, NY, USA*
[e]*Indian Institute of Technology, Delhi, India*
[f]*Fox Chase Cancer Center, Department of Urology, Philadelphia, PA, USA*

*Corresponding author. Department of Urology, University Hospitals of Cleveland, 11000 Euclid Avenue, Cleveland, OH 44106, USA. Tel. +1 2168443009.
E-mail address: laura.bukavina2@uhhospitals.org (L. Bukavina).

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Mapping Contemporary Biopsy Zones to Traditional Prostatic Anatomy: The Key to Understanding Relationships Between Prostate Cancer Topography, Magnetic Resonance Imaging Conspicuity, and Clinical Risk

Pranav Satish [a,b,], Benjamin Simpson [c], Alex Freeman [d], Francesco Giganti [b,e], Alex Kirkham [e], Clement Orczyk [b,f], Hayley Whitaker [b], Mark Emberton [b,f,†], Joseph M. Norris [b,f,†]*

The traditional zonal approach to prostate anatomy devised by McNeal in 1981 [1] was based on dividing the prostate into four histologically and anatomically distinct zones. Clinically, this zonal approach has proved to have utility in both benign and cancer urology, guiding diagnostic and treatment decisions. However, this simplistic zonal approach risks conveying an overly reductive representation of prostate anatomy and may be partly responsible for the paucity of data examining differences in subzonal prostate cancer risk and prognosis, compared to the relative abundance of data comparing these features between simple tumour zones [2,3]. Furthermore, classical transrectal ultrasound-guided biopsy may have contributed to the lack of detailed understanding regarding the influence of tumour zone of origin owing to well-acknowledged undersampling of the mid and anterior prostate [4].

In the PROMIS and PICTURE trials [5,6], a transperineal template mapping (TPM) biopsy technique was used as the diagnostic reference standard, in which prostate tissue was exhaustively interrogated at 5-mm intervals, providing a unique opportunity for subzonal analysis of prostate cancer topography.

The aim of our study was to map intricate biopsy information provided by modern transperineal biopsy protocols (eg, Barzell [7], Ginsburg [8]) to the traditional McNeal anatomical zones to create a bespoke tool designed to reveal important relationships between zones of tumour origin for a wealth of other potential outcomes, including tumour conspicuity on magnetic resonance imaging (MRI) and clinical risk, as derived from histopathological, genomic, and longitudinal correlates.

We used the traditional McNeal anatomical prostate zones as our ground truth, to which we mapped Barzell and

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European Association of Urology

Letter to the Editor

Re: Syed A. Hussain, Nuria Porta, Emma Hall, et al. Outcomes in Patients with Muscle-invasive Bladder Cancer Treated with Neoadjuvant Chemotherapy Followed by (Chemo)radiotherapy in the BC2001 Trial. Eur Urol 2021;79:307–15

The deductive principle of the fictional detective Sherlock Holmes of focussing on "what was missing rather than what was present" may be relevant to the analysis of the BC2001 data by Hussain et al [1].

Approximately 50% of patients with muscle-invasive bladder cancer have microscopic distant metastases at diagnosis and therefore there is a strong case for both local and systemic treatment [2]. In a post hoc analysis of the outcome for 117 patients who received neoadjuvant chemotherapy (NAC) before radiotherapy (RT) or concomitant chemoradiation (CRT), there was a statistically nonsignificant improvement in local control in the NAC + CRT arm ($p = 0.18$) but no difference in overall survival at 5 yr compared to patients receiving CRT only (48% vs 49%).

The possible problems associated with NAC are toxicity and the development of radioresistant tumour cells. There were slightly more acute and late grade $\geq$3 toxicities following NAC. Compared to the main trial population, the NAC subgroup were younger (66 vs 74 yr) and fitter (performance status [PS] 0: 73% vs 61%). It is disturbing that in spite of this apparent selection bias, the metastasis-free-survival was worse (54% vs 58%) with a higher rate of salvage cystectomy (21% vs 14%) in the NAC + CRT arm of the trial. Akin to the meticulous observation by Sherlock Holmes about the curious incident of the dog that didn't bark in the night-time, the fact that younger, fit patients with good PS did not have better survival, due to selection bias, should ring alarm bells.

In a meta-analysis of 21 trials of NAC in advanced cervix cancer treated with RT, dose-intense chemotherapy was associated with significantly better survival, but less intensive chemotherapy led to significantly worse survival than RT alone [3]. These differences in survival may be due to the development of radioresistant clones during less intense chemotherapy. While there is no firm evidence that this is the case in this small underpowered study, the possibility should be borne in mind.

Furthermore, the BC2001 subgroup analysis indicates that there is a ceiling to the beneficial effect of combining chemotherapy with radiotherapy (concurrent or neoadjuvant, but not both).

Baseline factors such as age, performance status and primary T stage were favourable in the NAC + CRT subgroup compared to NAC + RT subgroup (age 56 vs 61 yr; PS 0 70% vs 75%; stage T3/T4 14% vs 23%) but the overall survival of patients was broadly similar (48% vs 46%) [1]. This "missing" survival advantage due to imbalance in baseline factors again rings alarm bells.

The current bladder cancer guidance from the UK National Institute for Health and Care Excellence [4] advocates NAC followed by CRT, but the evidence base for this recommendation is small and not supported by the BC2001 data, in which there is a hint of a possibility of harm. While we agree with the authors' statement that "the role of neoadjuvant chemotherapy before chemoradiotherapy warrants further research in randomised trials", we wonder if the time for these trials is now past and the future emphasis should be on neoadjuvant immunotherapy or novel therapy before CRT [5].

Conflicts of interest: Santhanam Sundar has received advisory board and speaker fees and conference sponsorship from Bayer, BMS, Clovis Oncology, Pfizer, and Roche. Paul Symonds has nothing to disclose.?

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Santhanam Sundar[a,*]
Paul Symonds[b]

[a]*Nottingham University Hospitals NHS Trust, Nottingham, UK*
[b]*Leicester Cancer Research Centre, University of Leicester, Leicester Royal Infirmary, Leicester, UK*

*Corresponding author. Nottingham University Hospitals NHS Trust, Nottingham, UK.
E-mail address: sundar@oncology.org (S. Sundar).

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

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Letter to the Editor

Reply to Santhanam Sundar and Paul Symonds' Letter to the Editor re: Syed A. Hussain, Nuria Porta, Emma Hall, et al. Outcomes in Patients with Muscle-invasive Bladder Cancer Treated with Neoadjuvant Chemotherapy Followed by (Chemo)radiotherapy in the BC2001 Trial. Eur Urol 2021;79:307–15

We thank Santhanam Sundar and Paul Symonds for their interest in our article on outcomes in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy (NAC) followed by (chemo)radiotherapy in the BC2001 trial [1]. Our purpose in writing the manuscript was to explore the tolerability of chemoradiotherapy (cRT) after NAC and to explore if there was evidence of an additional benefit from cRT over radiotherapy when NAC was used. We were cognisant that this was a nonrandomised subgroup for which the choice of NAC use was subject to biases, in addition to limitations of statistical power. Thus, we deliberately avoided making comparisons between those who did and did not receive NAC, although we provided data for readers for reference in our Supplementary material [1].

Sundar and Symonds discuss the point that despite the age and performance status (PS) advantage (bias) in the NAC group, metastasis-free survival (MFS) is numerically worse than that observed in the whole population (54% vs 58%) and there were more salvage cystectomies. Owing to the different sample sizes for the groups from which both estimates were derived, the greater variability in the NAC subgroup needs to be factored in. Indeed, the 95% confidence interval (CI) for 5-yr MFS in the overall cRT subgroup is 50–65%, which includes the estimate of 54% observed for the NAC + cRT subgroup. We do not think that it can be inferred from our data that the 5-yr MFS in the NAC + cRT group is worse than in the overall cRT group.

The observation that the 5-yr rate of salvage cystectomy in the NAC + cRT group is higher than in the overall trial group can most likely be attributed to the younger age and better PS of the NAC cohort of patients. Younger and fitter patients are more likely to receive salvage cystectomy when required in comparison to older patients with poor PS and multiple comorbidities.

Although no statistically significant differences were found between cRT and RT for any of the endpoints, the magnitude of the treatment effect observed in the NAC cohort was comparable to that in the main trial across all outcomes (see the number of events and 5-yr estimates in Supplementary Table 3 [1]). Interestingly, the 5-yr rates of invasive locoregional control observed in both treatment groups in the NAC cohort were greater than those observed in the corresponding treatment groups in the main trial cohort.

Sundar and Symonds also expect to see a survival advantage in the NAC + cRT cohort in comparison to the NAC + RT cohort on the basis of "imbalance in baseline factors" such as age, PS, and primary T stage. This imbalance is evident between patients who had received prior NAC and those who did not (as shown in Supplementary Table 3 [1]) and it should be noted that we were not comparing these two groups of patients (where those imbalances would obviously have biased the observed outcome); rather, we focused on the cRT versus RT comparison within the NAC subgroup. Within this subgroup, and because randomisation in the BC2001 study was stratified by planned neoadjuvant treatment, cRT versus RT resulted in fairly well-balanced study groups.

Their observation that the age difference was 56 yr (NAC + cRT) versus 61 yr (NAC + RT) is factually inaccurate. These numbers are in fact the total number of patients (*n*) in each subgroup and not age. The median age in the NAC + cRT subgroup was 66.8 yr, compared to 64 yr in the NAC + RT subgroup. Likewise, PS 0 70% for NAC + cRT versus 75% for NAC + RT also favours the NAC + RT group. Lastly, 86% of patients in the NAC + cRT subgroup versus 77% in NAC + RT had stage T2 disease, favouring the NAC + cRT group, and we would accept this observation as such. We would also note that as this is a subgroup and hence not powered to assess survival differences.

We acknowledge the point that Sundar and Symonds make in their letter that such intense treatments have to be weighed carefully against the risk of toxicities given the lack of statistically significant overall survival benefit in this NAC subgroup analysis. It is notable that among patients in this cohort who received NAC and radical radiotherapy, the 5-yr overall survival rate was 46% (95% CI 33–58%) while that

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reported for radiotherapy alone in the main trial (including patients treated with or without NAC) was only 37% (95% CI 30–44%), a numerical difference that was not seen for cRT (48% neoadjuvant cohort; 49% main trial). However, we would caution against overinterpretation of these data given the broad CIs. The improvement in local control seen in our study in the subset of patients receiving NAC followed by RT alone is already supported by trial BA06, which yielded similar outcomes in this cohort [2]. There is insufficient power in this subanalysis to test the hypothesis of Sundar and Symonds concerning the "development of radioresistant clones" in patients receiving NAC followed by cRT (with different drugs), but we do question why any such effect should not also apply to the RT-only group equally. Our data confirmed that there was no compromise in the delivery of radical curative organ preservation treatment with the use of NAC, with a statistically nonsignificant improvement in local control without a detrimental effect on quality of life. We agree with the authors and support randomised trials testing neoadjuvant treatment approaches, including chemotherapy, novel agents, and immune checkpoint inhibitors [3–5].

Conflicts of interest: The authors have nothing to disclose.

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Syed A. Hussain[a*]
Nuria Porta[b]
Emma Hall[b]
Muneeb Qureshi[a]
Rebecca Lewis[b]
Robert Huddart[b]
Nicholas D. James[b]

[a]*Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK*
[b]*Institute of Cancer Research, Royal Marsden Hospital, London, UK*

[*]Corresponding author. Department of Oncology and Metabolism, University of Sheffield, Beech Hill Road, Sheffield, UK.
E-mail address: syed.hussain@sheffield.ac.uk (S.A. Hussain).

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Letter to the Editor

Re: Scott D. Lundy, Naseer Sangwan, Neel V. Parekh, et al. Functional and Taxonomic Dysbiosis of the Gut, Urine, and Semen Microbiomes in Male Infertility. Eur Urol 2021;79:826-36

The translational study conducted by Lundy and colleagues [1] compared the taxonomic and functional profiles of the gut, semen, and urine microbiomes of 25 men with primary idiopathic infertility with those of 12 healthy fertile controls prospectively enrolled. The authors identified a diverse semen microbiome with modest similarity in terms of urinary microbiome, with infertile men having a specific microbial profile specifically associated with semen quality. Metagenomics data identified significant alterations in the *S*-adenosyl-L-methionine cycle, which could be involved in the pathogenesis of infertility via DNA methylation, oxidative stress, and/or polyamine synthesis [1].

The authors should be commended for completing this pilot study, which represents one of the few available comprehensive investigations of microbiomes in the context of male infertility. The rationale for investigating the gut, semen, and urinary microbiomes between men with idiopathic infertility and fertile controls is intriguing. However, some points deserve major discussion. First, idiopathic infertility as defined in the current study does not adhere to the current European Association of Urology guidelines definition ("men presenting with no previous history of diseases affecting fertility and with normal findings on physical examination and endocrine, genetic and biochemical laboratory testing" [2]), since men with varicocele, a history of gonadotoxin exposure, and receipt of remote testosterone therapy were also included. Second, we argue that the analysis of the semen microbiome carries relevant limitations in terms of contamination from the urinary tract and the skin. In this context, no sufficient data have been provided to allow a crystal-clear dichotomy in terms of sampling among different topographic sections throughout the genitourinary system. Third, the semen microbiome poorly targets the intratesticular environment, as prostatic and seminal vesicles are the main contributors to semen production. A recent systematic review found that evidence regarding the impact of the seminal microbiome on fertility is inconclusive [3], possibly reflecting the aforementioned limitations.

We suggest that the intratesticular microbiome might be a more appropriate and accurate research focus, although it is definitely more challenging to harvest biological (and properly obtained) material in this setting. In this regard, Alfano et al [4] found that the human testicular microenvironment is not microbiologically sterile and that among men with idiopathic nonobstructive azoospermia (iNOA) there is even bacterial dysbiosis between those with negative and those with positive sperm retrieval at microdissection testicular sperm extraction (microTESE). Likewise, bacterial dysbiosis was identified between iNOA men and normozoospermic men who were undergoing orchiectomy [4]. Normozoospermic patients had Actinobacteria, Bacterioidetes, Firmicutes, and Proteobacteria as the dominating phyla. Conversely, Actinobacteria and Firmicutes were dominant among those with iNOA [4]. Lastly, the authors used metagenomics data to identify significant alterations in the *S*-adenosyl-L-methionine cycle, which is involved in DNA methylation, oxidative stress, and/or polyamine synthesis. We believe that the proteome also plays a major role in male infertility, as a pathogenetic signature of the somatic human testicular microenvironment has been identified, providing two vitamin-related mechanistic insights into the molecular determinants of idiopathic germ cell aplasia [5].

Conflicts of interest: The authors have nothing to disclose.

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Eugenio Ventimiglia[a,†]
Edoardo Pozzi[a,b,†]
Massimo Alfano[a]
Francesco Montorsi[a,b]
Andrea Salonia[a,b*]

[a]*Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy*
[b]*Università Vita-Salute San Raffaele, Milan, Italy*

*Corresponding author. Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26435506; Fax: +39 02 26432969.
E-mail address: salonia.andrea@hsr.it (A. Salonia). †These authors contributed equally to this work.

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Letter to the Editor

Reply to Eugenio Ventimiglia, Edoardo Pozzi, Massimo Alfano, Francesco Montorsi, and Andrea Salonia's Letter to the Editor re: Scott D. Lundy, Naseer Sangwan, Neel V. Parekh, et al. Functional and Taxonomic Dysbiosis of the Gut, Urine, and Semen Microbiomes in Male Infertility. Eur Urol 2021;79:826–36

We read with interest the letter from Ventimiglia and colleagues in response to our recent manuscript in *European Urology* [1] and appreciate the opportunity to clarify several of the insightful points raised by this group.

Regarding the inclusion criteria, we intentionally chose to include men with varicocele in this study because of the high prevalence and poorly understood pathophysiology associated with this condition. Some 85% of men with varicocele experience no difficulty with fertility [2], and it remains critically important to better understand why varicocele is pathologic in only a subset of men. The data presented in our study support our initial hypothesis that varicocele shifts the microbiome from aerobic symbiosis to anaerobic dysbiosis in the subset of men who develop subfertility and provides a novel mechanistic basis that may help to explain the broad spectrum of clinical presentation . Larger studies to confirm this finding and explore the underlying mechanisms and therapeutic opportunities are currently under way.

The authors assert that direct measurement of the intratesticular microbiome is a more appropriate research focus than assessment of the seminal microbiome. While direct testicular interrogation can certainly provide important hypothesis-generating basic science information, the ethical challenges associated with invasively sampling healthy testicles as a suitable control remain difficult to overcome. Indeed, the group's recent manuscript [3] compared the taxonomic 16S microbiome in men with nonobstructive azoospermia to that of "non-neoplastic specimens" obtained from testicles being removed for malignancy (seminoma). Despite taking samples from a histologically normal region of the cancerous testicle, previous studies by our group [4] and others [5] have demonstrated profound microbiome differences—even in adjacent normal tissue—in the setting of malignancy. Thus, while the finding of altered genus-level taxonomy in men with azoospermia is provocative, further studies with more rigorous controls will be necessary to assess the role of the intratesticular microbiome in spermatogenesis. In addition, at present, assessment of the intratesticular milieu can only be achieved at the time of an invasive surgical intervention. We would argue that from a translational perspective, analysis of semen samples is faster and easier and may provide greater clinical diagnostic value in guiding initial treatment before the need for surgical management.

Moving beyond these initial proof-of-principle studies [1,3], we agree with the assertion that the role of -omics approaches such as proteomics, and more broadly speaking "multi-omics" integration, is a logical evolution [6]. Our institute has published extensively on the proteome in male infertility [7] and varicocele [8], the transcriptome in genitourinary malignancy [9], and the metabolome in stone disease [10], and we will continue to explore approaches to integration of these techniques in a unified framework to better understand these complex urologic conditions.

In summary, we eagerly anticipate future thought-provoking work by this Italian group and many others in this field as we strive towards a better understanding of male infertility through next-generation sequencing and -omics approaches.

***Conflicts of interest*:** The authors have nothing to disclose.

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Scott D. Lundy[a,b,*]
Sarah C. Vij[a]
Charis Eng[b,c]

[a]*Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA*
[b]*Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA*
[c]*Department of Genetics and Genome Sciences and Germline High Risk Cancer Focus Group, Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA*

*Corresponding author. Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel. +1 216 3796134; Fax: +1 216 4452267.
E-mail address: lundys@ccf.org (S.D. Lundy).

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European Association of Urology

Letter to the Editor

Re: Sophie Knipper, Luigi Ascalone, Benjamin Ziegler, et al. Salvage Surgery in Patients with Local Recurrence After Radical Prostatectomy. Eur Urol 2021;79:537–44

Surgical resection of local recurrence of prostate cancer after radical prostatectomy (with or without adjuvant or salvage radiotherapy) is an attractive option for selected patients seeking an alternative to systemic therapy. We would like to congratulate Knipper et al [1] on the impressive series of 40 patients treated with salvage open surgery; the initial outcomes reported are encouraging and similar to our initial personal experience. To date, we have performed 15 resections of local recurrence using the robotic approach and the data will be published once longer follow-up is available.

We are disappointed that the authors failed to identify our initial publication; in 2019 we published our initial experience with two cases of robot-assisted laparoscopic resection of prostate cancer local recurrence following radical prostatectomy and salvage radiotherapy [2]. In our two cases, magnetic resonance imaging showed a solid mass in the prostatic fossa and positron emission tomography/computed tomography revealed significant local uptake of prostate-specific membrane antigen ligand. Imaging-guided biopsy was performed before salvage surgery in both cases to confirm local recurrence. The robotic approach was selected on the basis of surgeon experience (R.F.C.) and imaging quality and the surgical precision of the da Vinci system. Both surgeries were uneventful, both patients recovered well with no impact on their urinary continence, and after a short 6-mo period of follow-up, both had prostate-specific antigen $<$1.5 ng/ml. A video showing intraoperative findings and the surgical approach is attached to our published paper [2]. The results presented by Knipper et al [1] are more mature than our series and could encourage more surgeons to adopt this technique for selected patients using either open or robot-assisted surgery. However, the sentence “We are the first to describe this procedure in the salvage setting” is not accurate and the authors should acknowledge our publication available on PubMed since 2019.

Conflicts of interest: The authors have nothing to disclose.

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Fabio C.M. Torricelli[a*]
Rafael F. Coelho[ab]

[a]*Division of Urology, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil*
[b]*Instituto do Cancer do Estado de São Paulo, Sao Paulo, Brazil*

*Corresponding author. Division of Urology, Hospital das Clinicas, University of Sao Paulo Medical School, Avenida Vereador Jose Diniz 3300, 04604-006 Sao Paulo, Brazil. Tel. +55 11 27684552.
E-mail address: fabio.torricelli@hotmail.com (F.C. Torricelli).

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European Association of Urology

Letter to the Editor

Reply to Fabio C.M. Torricelli and Rafael F. Coelho's Letter to the Editor re: Sophie Knipper, Luigi Ascalone, Benjamin Ziegler, et al. Salvage Surgery in Patients with Local Recurrence After Radical Prostatectomy. Eur Urol 2021;79:537–44

We thank Torricelli and Coelho for their important remark regarding their initial experience in robot-assisted salvage surgery for local recurrence in a case series of two patients [1]. The short-term outcomes were quite promising and we look forward to publication of their further experience and longer follow-up. We also hope that both our and their experiences will encourage more surgeons to adopt this salvage surgery technique for highly selected patients experiencing local recurrence of prostate cancer after radical prostatectomy, using either an open or robot-assisted approach [2].

Conflicts of interest: The authors have nothing to disclose.

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Sophie Knipper[a*]
Tobias Maurer[ab]

[a]*Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany*
[b]*Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany*

*Corresponding author. Martini-Klinik Prostate Cancer Center, University Hospital Hamburg—Eppendorf, Martinistraße 52, 20246 Hamburg, Germany.
E-mail address: a.knipper@uke.de (S. Knipper).

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European Association of Urology

Letter to the Editor

Re: Paul Abrams, Lynda D. Constable, David Cooper, et al. Outcomes of a Noninferiority Randomised Controlled Trial of Surgery for Men with Urodynamic Stress Incontinence After Prostate Surgery (MASTER). Eur Urol 2021;79:812–23

We read with great interest the results from the recently published MASTER trial reported by Abrams et al [1]. The authors compared male slings to artificial urinary sphincters (AUS) in men with urodynamic-proven stress incontinence after prostate surgery. They confirm, using a composite primary endpoint of patient-reported (in)continence at 12 mo, that male sling surgery (87% incontinence) is noninferior to AUS (84% incontinence) in this population. Since randomised controlled trials (RCTs) and urologic surgery are a rare combination, we can only congratulate the authors on their tremendous effort in trying to clarify this relevant topic.

The investigators have chosen a very strict primary endpoint. The definition is so strict that only 13% of men in the sling group and 16% in the AUS group are considered continent. By contrast, the secondary outcome of satisfaction shows that 90% of men were satisfied in the AUS group versus 72% in the sling group. The selection of this primary endpoint raises several problems. First, the study was powered for the assumption that an 80% continence rate would be observed at 12 mo. Although the number of patients needed to achieve the noninferiority margin of 15% might not change dramatically, the 15% continence rate found is far below the success rate assumed before the study start. Second, the study risks being misinterpreted. Who would accept a surgery with a chance of failure of >80%. In this interpretation, both surgeries fail and one just does not fail to a worse extent than the other. This is in sharp contrast to the satisfaction rates. One could even argue that these satisfaction rates are caused by cognitive dissonance rather than by effective treatment. It would have been better to have chosen a clinically more meaningful primary outcome. This point stresses our communal failure as urologists to address outcomes in functional urology in a harmonised and standardised way.

The investigators allowed irradiated patients (n = 77), patients with high amounts of urine loss (>250 g/24 h; n = 158), and patients with resolved bladder neck contracture (number not reported) to enrol in the trial, underlining the importance of a real-life study that could serve as guidance for clinicians during counselling. The rationale for allowing these patients to enrol in the study was that there are no adequate quality data in the literature to be able to write inclusion and exclusion criteria, and that individuals should not be excluded "unless there were clear safety issues of convincing data on poor outcome". Although we agree with the absence of safety concerns, we argue that we do have evidence of a negative effect of some of these characteristics on the outcomes of sling surgery. In several cohort studies, multivariate analysis has shown significant and strong association of irradiation and previous bladder neck contracture treatment [2–5]. In our own observations for 216 sling treatments, multivariate analysis showed that both previous irradiation (hazard ratio [HR] 3.4, 95% confidence interval [CI] 1.9–6.0) and previous bladder neck treatment (HR 2.4, 95% CI 1.3–4.6) were independently associated with sling failure (our own data). Our current clinical practice is more fine-tuned, as some patients will probably not benefit from surgery in this scenario. It would have been better for a first-in-kind trial to exclude these patients from the population. We do not agree that "there is now good-quality evidence from the PROMS to show that even men with greater leakage can be offered the sling procedure, after full discussion of the findings of MASTER, as most men are satisfied with a sling. When we tested for a difference between the <250 g and >250 g leakage levels, on the baseline 24-h pad tests, the effect size was 0.62 (0.16, 2.36; p = 0.4)." The trial was not powered to be able to make this statement.

We also argue that catheterisation for high postvoid residual volume monitored during postoperative follow-up is not a serious adverse event. Even if catheterisation is accompanied by a prolonged hospitalisation, it is not associated with a serious deterioration in health as stated in the European Commission classification [6]. In our own series we have a recatherisation rate of up to 20%. The majority of patients are taught clean intermittent self-catheterisation (CISC) and leave the hospital on the same day. In general, these patients perform CISC for 1–3 d.

This trial opens a discussion on the place of registries and RCTs in surgery. RCTs should unarguably be part of clinical science in surgery. They should be adopted more frequently and earlier in the course of new treatments. In our centre, the first male sling was implanted in 2007. In common with many other urologists, we have used this device for 14 yr in

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the absence of RCT data. We feel confident (through prospective and retrospective monitoring of our results) that the benefits of our interventions (both sling and AUS) outweigh the harms. The MASTER trial data also do not suggest that a medical reversal is in the making, but the long time lag between market approval and the first well-powered RCT is staggering. Times have changed. We are currently participating in prospective registries for marketed devices and RCTs for premarket devices. Safety profiles of similar devices can be derived from well-conducted registries, but to prove specific benefits in specific populations, RCTs are indispensable. We hope that the MASTER trial has set the scene for the future.

Conflicts of interest: The authors have nothing to disclose.

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Frank Van der Aa[a]
Yves Deruyver[a]
Manuela Tutolo[ab,*]
[a]*Department of Urology, UZ Leuven, Leuven, Belgium*
[b]*Division of Oncology, Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy*

*Corresponding author. Department of Urology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel. +32 16 346930; Fax: +32 16 346931.
E-mail address: tutolo.manuela83@gmail.com (M. Tutolo).

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European Association of Urology

Letter to the Editor

Re: Sophie Knipper, Luigi Ascalone, Benjamin Ziegler, et al. Salvage Surgery in Patients with Local Recurrence After Radical Prostatectomy. Eur Urol 2021;79:537–44

Knipper et al [1] present data on local recurrences after radical prostatectomy and salvage surgery in the former seminal vesicle bed. For better identification, surgery was performed using a radioguided technique, with which the study group is very experienced. Although more than 80% of the cohort received any kind of radiotherapy, obviously recurrent disease developed. Underlined by a surgical video, the authors highlight the feasibility of resecting local recurrences without significant morbidity and with acceptable short-term oncologic control. As positron emission tomography (PET) diagnostics are increasingly available, such local recurrences are described more often and publications are available. All the existing data show that recurrences in such a location are not isolated local recurrences, but most likely are recurrent disease in the seminal vesicle remnants [2,3]; we also assume this finding from the analysis. If we consider that more than 50% of the patients in the present and other series had locally advanced disease at the time of surgery, we have to assume that radical prostatectomy was not properly performed initially. Wymer et al [2] were the first to describe resections of either seminal vesicle remnants after radical prostatectomy or isolated recurrent disease after radiotherapy with a prostate-sparing seminal vesicle resection. It has been proposed that local salvage radiotherapy in recurrent disease of the seminal vesicles needs a rather high dosage of 76 Gy to achieve local control of $>$90% after 5 yr. However, the associated toxicity is significantly higher. More than one-third of patients receiving such doses suffered from grade $\geq$2 toxicities [4]. As the majority of the patients in the three available series had prior radiotherapy, surgical resection should be the treatment of choice if PET diagnostics indicate seminal vesicle remnants. Systemic treatment can be considered, but in our experience there is a risk of predominantly local progressive disease under either chemotherapy or next-generation androgen manipulation or both, with a need for postponed surgery in castration-resistant disease. In our experience, all patients will develop biochemical relapse with longer follow-up; surgery in this setting must be viewed as preventive for local symptoms [3]. Knipper et al demonstrate radioguided surgery in this setting, which is undoubtedly possible. This procedure has significantly improved the detection rate of lymph node metastases in salvage lymph-node dissection series, with improvements in prostate-specific antigen responses [5]. In cases of seminal vesicle resection, anatomic structures such as the ductus deferens and the size of the recurrence usually make identification and resection comfortable, as nicely demonstrated in the video. Therefore, radioguided surgery in this setting is less informative than in salvage lymph-node dissection and can be spared. Owing to the easy transabdominal access, laparoscopic and robot-assisted series can be considered in the near future.

Conflicts of interest: The authors have nothing to disclose.

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David Pfister*
Florian Hartmann
Axel Heidenreich
Department of Urology, Uro-Oncology and Robot-Assisted Surgery, University Hospital of Cologne, Cologne, Germany

*Corresponding author. Department of Urology, Uro-Oncology and Robot-Assisted Surgery, University Hospital of Cologne, Kerpener Strasse 62, Cologne 50937, Germany.
E-mail address: david.pfister@uk-koeln.de (D. Pfister).

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European Association of Urology

Letter to the Editor

Re: Stanley Weng, Renzo G. DiNatale, Andrew Silagy, et al. The Clinicopathologic and Molecular Landscape of Clear Cell Papillary Renal Cell Carcinoma: Implications in Diagnosis and Management. Eur Urol 2021;79:468–77

We read with interest the recent study by Weng and colleagues [1] regarding the clinicopathologic features and molecular landscape of clear-cell papillary renal cell carcinoma (CCPRCC). They state, "Interestingly, a recently published case report describes a potential case of metastatic CCPRCC. However, the primary tumor was not evaluated, nor was a comprehensive molecular analysis performed to rule out overlapping entities (eg, *TCEB1*-mutant or *TSC*-associated RCC). *TCEB1*-mutant tumors, which have been shown to have metastatic potential, can be mistaken for CCPRCC due to the presence of similar morphologic and IHC characteristics, such as focal linear arrangement of nuclei, as well as CA-IX and CK7 positivity. However, loss of chromosome 8 can be used to distinguish *TCEB1*-mutant RCC from CCPRCC, a feature that was present in the reported 'metastatic CCPRCC' case."

As the authors have pointed out, it has been shown that *TCEB1*-mutant tumors have metastatic potential; however, only two cases of metastatic *TSC1/2*-mutated RCC with clear cell features have been reported in the English language literature and these tumors were found to involve regional lymph nodes in both cases [2,3]. To date, no visceral or distant metastasis has been reported for *TSC1/2*-mutated RCC with clear cell features and such tumors are regarded as being indolent [3]. We would like to confirm that next-generation sequencing (NGS) using the clinically validated MayoComplete Solid Tumor Panel that interrogates 514 genes identified a hotspot *TERT* promoter alteration at position −124; however, no other pathogenic alterations were identified for the genes tested, including *VHL*, *TSC1*, *TSC2*, and *TCEB1* (*ELOC*) (tumor mutation burden: 0.8 mutations/megabase; microsatellite stable). Furthermore, in their prior study, the authors suggested that CCPRCCs potentially arise from the distal nephron and frequently exhibit diffuse positivity for markers such as GATA3/HMWCK, as opposed to clear cell RCC [1,4]. By contrast, HMWCK positivity was reported for only one (of 8) *TCEB1*-mutant RCC (focally, 10% of the tumor) by the authors themselves [5]. Of note, the tumor reported by us showed diffuse positivity for both GATA3 and HMWCK, and this immunophenotype is more supportive of a CCPRCC than a *TCEB1*-mutant RCC.

In conclusion, we would like to point out that in our clinical practice we routinely attempt to histologically subtype metastatic RCC. Although no *VHL*, *TSC1*, *TSC2*, or *TCEB1* alterations were identified for this case, definitive exclusion of an underlying pathogenic molecular event would require promoter methylation studies to exclude gene silencing as well, and these studies were not pursued on account of cost. This highlights the objective of the case report: to what extent should we pursue expensive molecular analyses in routine clinical practice for these indolent tumors? [6] We agree that a definitive determination is not possible in the absence of further molecular profiling; however, we would like to emphasize that, in our opinion, the combined immunophenotype, virtual karyotype, and molecular profile of this tumor does not fit what has been commonly described for clear cell RCC, *TSC1*/*TSC2*-mutated, or *TCEB1*-mutant RCC.

Conflicts of interest: The authors have nothing to disclose.

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Sounak Gupta*
Beth A. Pitel
Shannon M. Knight
Kevin C. Halling
Rafael E. Jimenez
John C. Cheville
Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

*Corresponding author. Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA. Tel. +1 507 2841265; Fax: +1 507 2840590.
E-mail address: gupta.sounak@mayo.edu (S. Gupta).

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

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Corrigendum

Corrigendum re: "Robot-assisted Level II–III Inferior Vena Cava Tumor Thrombectomy: Step-by-Step Technique and 1-Year Outcomes" [Eur Urol 2017;72:267–74]

Sameer Chopra [a,†], *Giuseppe Simone* [b,†], *Charles Metcalfe* [a,†], *Andre Luis de Castro Abreu* [a], *Jamal Nabhani* [a], *Mariaconsiglia Ferriero* [b], *Alfredo Maria Bove* [a], *Rene Sotelo* [a], *Monish Aron* [a], *Mihir M. Desai* [a], *Michele Gallucci* [b], *Inderbir S. Gill* [a,*]

[a] *USC Institute of Urology, Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [b] *"Regina Elena" National Cancer Institute, Rome, Italy*

We report a few inadvertent errors that we recently discovered in our multicenter retrospective case series. These errors were identified while our team was working on a subsequent manuscript on a related topic. The original and corrected data are presented below. Total number of patients: $n = 22$ (previously $n = 24$); thrombus level II: $n = 10$, 45% (previously $n = 13$, 54.2%); thrombus level III: $n = 12$, 55% (previously $n = 11$, 45.8%); operative time: median 4.9 h, range 3–10.7 (previously median 4.5 h, range 3–8); estimated blood loss: median 325 ml, range 100–8000 (previously median 240 ml, range 100–7000); patients receiving intraoperative transfusion: $n = 7$, 31.8% (previously $n = 5$, 20.8%); postoperative hospital stay: median 4 d, range 1–22 (unchanged from original); and complications: $n = 4$ (unchanged from original), with one patient each developing a Clavien 2, 3a, 3b, and 4a complication (previously Clavien 2 [$n = 2$], 3a [$n = 1$], and 3b [$n = 1$]).

Although these are minor changes in recalculated median (range) values, our core message, robotic technique, and the tone and substance of our original manuscript, which reported the largest series of robotic level III inferior vena cava thrombectomy cases in the literature at that time of writing, remain unchanged. In addition, our conclusion that our "encouraging early experience provides confidence that the requisite vascular, reconstructive, and oncologic surgical principles and technical nuances can be reliably and reproducibly addressed robotically with good clinical outcomes" remains unchanged.

Conflicts of interest: Mihir M. Desai declares conflict of interest for Hansen Medical, Auris Robotics, Procept Biorobotics, and Baxter. Inderbir S. Gill declares conflict of interest for Steba Biotech (Unpaid Advisor).

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* Corresponding author. USC Institute of Urology, 1441 Eastlake Avenue, Suite 7416, Los Angeles, CA 90089, USA. Tel. +1 323 8653794; Fax: +1 323 8650120.
E-mail address: gillindy@gmail.com (I.S. Gill).
† These authors contributed equally to this manuscript.

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CONGRESS CALENDAR

3.9–4.9.2021 **Virtual online meeting**	22nd Meeting of the European Association of Urology Nurses: EAUN21	**Contact:** Congress Consultants B.V. E-mail: eaun@uroweb.org Tel.: +31 26 3891751 Website: www.eaun21.org
4.9.2021 **Vienna** Austria	ESU course on Prostate Cancer: Treatment for Biochemical Recurrence After Local Therapy and for Oligometastatic Disease to be held during CEM21 meeting	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org
17.9.2021 **Belgrade** Serbia	ESU course to be held during the National Congress of the Serbian Urological Association	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org
17.9.2021 **Stuttgart** Germany	ESU course on New Technologies in Urology to be held during the National Congress of the German Association of Urology	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org
23.9.2021 **St. Petersburg** Russia	ESU course to be held during the National Congress of the Russian Society of Urology	**Contact:** Russian Society of Urological Oncology (ROOU) Email: roou@roou.ru Website: https://roou.ru
6.10–7.10.2021 **Madrid** Spain	ESU-ESAU-ESGURS Masterclass on Erectile Restoration and Peyronie's disease	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.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
8.10–9.10.2021 **Madrid** Spain	12 Meeting of the EAU Section of Genito-Reconstructive Surgeons (ESGURS21)	**Contact:** Congress Consultants B.V. E-mail: info@congressconsultants.com Tel.: +31 26 3891751 Website: www.esgurs21.org
16.10.2021 **Virtual online event**	EAU Update on Prostate Cancer: PCa21	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.pca21.org
22.10.2021 **Virtual online event**	ESU course to be held during the National Congress of the Tunisian Urological Association	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org
28.10–29.10.2021 **Madrid** Spain	ESU-ESTU Masterclass on Kidney Transplant	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.uroweb.org
29.10.2021 **Lima** Peru	8th Confederacion Americana de Urologia Residents Education Programme (CAUREP)	
4.11–5.11.2021 **Nijmegen** The Netherlands	ESU-ESFFU Masterclass on Functional Urology	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.uroweb.org

8.11.2021 **Tashkent** Uzbekistan	ESU course to be held during the National Congress of the Scientific Society of Urologists of Uzbekistan	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org
11.11–13.11.2021 **Dusseldorf** Germany	18th Meeting of the EAU Robotic Urology Section in conjunction with the 13 Meeting of the German Society of Robotic Urology (ERUS-DRUS21)	**Contact:** Congress Consultants B.V. E-mail: info@congressconsultants.com Tel.: +31 26 3891751 Website: https://erus.uroweb.org/
18.11–19.11.2021 **Barcelona** Spain	ESU-ESUT Masterclass on Lasers in Urology	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://esu-masterclasses.uroweb.org/
25.11.2021 **Athens** Greece	9th Meeting of the EAU Section of Urological Imaging (ESUI21)	**Contact:** Congress Consultants B.V. E-mail: info@congressconsultants.com Tel.: +31 26 3891751 Website: www.esui.org
25.11–28.11.2021 **Athens** Greece	13th European Multidisciplinary Congress on Urological Cancers (EMUC21; hybrid physical/virtual meeting)	**Contact:** Congress Consultants B.V. E-mail: info@congressconsultants.com Tel.: +31 26 3891751 Website: https://emuc.org/
7.12–9.12.2021 **Berlin** Germany	ART in Flexible – Steps 1 & 2	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: https://artinflexible.uroweb.org/
9.12–10.12.2021 **Madrid** Spain	ESU-ESTU Masterclass on Kidney Transplant	**Contact:** European School of Urology (ESU) Tel.: +31 26 3890680 E-mail: esu@uroweb.org
21.1–23.1.2022 **Madrid** Spain	19th Meeting of the EAU Section of Oncological Urology	**Contact:** European Association of Urology Tel.: +31 26 3890680 E-mail: ESOU@congressconsultants.com Website: esou22.org
4.2–9.2.2022 **Prague** Czech Republic	19th European Urology Residents Education Programme (EUREP)	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.eurep22.org
24.2–25.2.2022 **Prague** Czech Republic	ESU-ESOU Masterclass on Non–muscle-invasive Bladder Cancer	**Contact:** European School of Urology Tel.: +31 26 3890680 E-mail: esu@uroweb.org Website: www.esunmibc.org