Indexed in Embase, Excerpta Medica Database, Scopus Elsevier Database and Emerging Sources Citation Index (ESCI), a new edition of Web of Science

Special Issue

Urologic problems in elderly patients

Guest Editor

Riccardo Autorino
Editorial Board

Editor-in-Chief
Gianluigi Vendemiale – Foggia, Italy

Former Editor
Mario Barbagallo – Palermo, Italy

Deputy Editor
Luigi Iuliano – Roma, Italy

Managing Editor
Francesco Bellanti – Foggia, Italy

Honorary Editors
Pier Ugo Carbonin – Roma, Italy
Gaetano Crepaldi – Padova, Italy
Giulio Massotti – Firenze, Italy
Francesco Balsano – Napoli, Italy
Gianfranco Salvioni – Modena, Italy
Umberto Serin – Perugia, Italy

Senior Editors
Roberto Bernabei – Roma, Italy
Sergio Della Sala – Edinburgh, UK
Paul Edison – London, UK
Nicola Ferrara – Napoli, Italy
Luigi Ferrucci – Baltimore, USA
Paul Francis – London, UK
Laura Frattiglioni – Stockholm, Sweden
Walter J. Koch – Philadelphia, USA
Nicolò Marchionni – Firenze, Italy
Jean-Pierre Michel – Geneve, Switzerland
Giuseppe Paolissio – Napoli, Italy
Nicola Pavese – London, UK
Munir Pirmohamed – Liverpool, UK
Giuseppe Poli – Torino, Italy
Michele Tagliati – Los Angeles, CA, USA
Marco Trabucchi – Brescia, Italy
José Vina Ribes – Valencia, Spain

Associate Editors
Biogerontology
Ettore Bargamini – Pisa, Italy
Tommaso Cassano – Foggia, Italy
Graziamaria Corbi – Campobasso, Italy
Mauro Di Bari – Firenze, Italy
Claudio Franceschi – Bologna, Italy
Anna Maria Giudetti – Lecce, Italy
Fabrizia Lattanzio – Ancona, Italy
Dario Leosco – Napoli, Italy
Patrizio Odetti – Genova, Italy
Maria Cristina Polidoro – Köln, Germany

Clinical Geriatrics
Angela Marie Abbatecola – Ancona, Italy
Pasquale Abete – Napoli, Italy
Giorgio Annovì – Milano, Italy
Raffaele Antonelli Incalzi – Roma, Italy
Lodovico Bollducchi – Tampa, Florida, US
Michelangelo Barbieri – Napoli, Italy
Mario Belvedere – Palermo, Italy
Bruno Bernardini – Padova, Italy
Marco Bertolotti – Modena, Italy
Angelo Blanchetti – Brescia, Italy
Massimo Calabro’ – Treviso, Italy
Vincenzo Canonicco – Napoli, Italy
Cristian Capurso – Foggia, Italy
Giovanna Elisenda Carpenago – Foggia, Italy
Michele Cassano – Foggia, Italy
Giampaolo Ceda – Parma, Italy
Alberto Cester – Mirano (Ve), Italy
Antonio Cherubini – Perugia, Italy
Francesco Corica – Messina, Italy
Andrea Corsonello – Ancona, Italy
Domenico Cucinotta – Messina, Italy
Walter De Alfieri – Grosseto, Italy
Ligia Juliana Dominguez Rodriguez – Palermo, Italy
Lorenzo Maria Donini – Roma, Italy
Paolo Falaschi – Roma, Italy
Giovanni Gambassi – Roma, Italy
Antonio Guatì – Abategrasso, Italy
Giancarlo Isaia – Torino, Italy
Giuseppe Landi – Roma, Italy
Maria Lia Lunardelli – Bologna, Italy
Marciole Giuseppe Maggio – Parma, Italy
Enzo Manzato – Padova, Italy
Daniele Mari – Milano, Italy
Francesco Mattace Raso – Rotterdam, The Netherlands
Domenico Maugeri – Catania, Italy
Riccardo Memeo – Acquaaviva delle Fonti (BA), Italy
Chiara Mussi – Modena e Reggio Emilia, Italy
Claire Nicholl – Cambridge, UK
Gabriele Noro – Trento, Italy
Emanuela Orsi – Milano, Italy
Ernesto Palummini – Genova, Italy
Giuseppe Pergo – Napoli, Italy
Giovanni Ricciuti – Pavia, Italy
Maria Rosaria Rizzo – Napoli, Italy
Giuseppe Romanelli – Brescia, Italy
Antonino Davide Romano – Foggia, Italy
Renzo Rozzini – Brescia, Italy
Afro Salsi – Bologna, Italy
Giuseppe Sergi – Padova, Italy
Sebastiano Bruno Solerte – Pavia, Italy
Vincenzo Soffritti – Bari, Italy
Gabriele Toigo – Trieste, Italy
Maristerea Ventura – Bari, Italy
Stefano Volpato – Ferrara, Italy
Giuseppe Zuccala – Roma, Italy
Giovanni Zuliani – Ferrara, Italy

Geriatric Nursing
Nicoletta Nicelli – Torino, Italy
Erminelia Zanetti – Brescia, Italy

Psychosocial Gerontology
Luísia Bartorelli – Roma, Italy
Orazio Zanetti – Brescia, Italy

Statistical Analysis and Trials
Corrado Crocetta – Foggia, Italy
Elia Pio Navarrese – Virginia, USA

Scientific secretariat
Valentina Bärberi
Journal of Gerontology and Geriatrics
Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 3130376 - Fax +39 050 3130300
secretary@jgerontology-geriatrics.com

Società Italiana di Gerontologia e Geriatria
Via G.C. Vanini 5, 50129 Firenze, Italy
Tel. +39 055 474330 - Fax +39 055 461217
E-mail: sigg@sigg.it - www.sigg.it

© Copyright by
Società Italiana di Gerontologia e Geriatria

Managing Director
Raffaele Antonelli Incalzi

Publisher
Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 3130300
info@pacinieditore.it

Published online by Pacini Editore Srl,
Pisa, December 2018.
online: www.jgerontology-geriatrics.com

Authors Informations
www.jgerontology-geriatrics.com/category/author-sinfirmation/

Submission online
submission.jgerontology-geriatrics.com

Journal registered at “Registro pubblico degli Operatori della Comunicazione” (Pacini Editore Srl registration n. 6269 - 29/8/2001), The Publisher remains at the complete disposal of those with rights whom it was impossible to contact, and for any omissions. Subscriber data are treated according to Italian law in Dgs. 3 June 2003, n. 106 as updated with the UE General Data Protection Regulation 2016 - by means of computers operated by specifically responsible personnel. These data are used by the Publisher to mail this publication. In accordance with Art. 7 of the above mentioned Dgs, 3 June 2003, n. 106, subscribers can, at any time, view, change or delete their personal data or withdraw their use by writing to Pacini Editore S.r.l. - Via A. Gherardesca 1, 56121 Pisa (Italia), for further information refer to the website: http://www.jgerontology-geriatrics.com/informativa-privacy-policy/ Photocopies, for personal use, are permitted within the limits of 15% of each publication by following payment to SIAE of the charge due, article 63, paragraphs 4 and 5 of the Law April 22, 1941, No 633. Reproductions for professional or commercial use or for any other purpose other than personal use can be made following a written request and specific authorization in writing from AIDRO, Corso di Porta Romana, 108, 20122 Milan, Italy (segreteria@aidro.org - www.aidro.org).
Special Issue
Urologic problems in elderly patients

Guest Editor
Riccardo Autorino

Original Investigations
Elderly patients and prostate biopsy. How old is too old?

Elderly patients are not at higher risk of urinary incontinence after radical prostatectomy
N. d’Altilia, M. Di Nauta, U.G. Falagario, B. Calò, O. Selvaggio, F. Sanguedolce,
V. Mancini, G. Stallone, E. Barret, L. Cormio, G. Carrieri .................................................... 168

Is percutaneous nephrolithotomy effective and safe in elderly patients?
Outcomes of a case-control study
A. Mangiatordi, M. Auciello, G. Stallone, A. Saita, A. Hoznek, L. Cormio .............................. 173

Prostatic inflammation is associated with benign prostatic hyperplasia rather than prostate cancer
U. Falagario, O. Selvaggio, G. Carrieri, E. Barret, F. Sanguedolce3 L. Cormio ....................... 178

Short Communications
Treating high-grade T1 bladder cancer in the elderly. Is intravesical instillation of BCG worth?
B. Calò, M. Di Nauta, V. Mancini, A. Hoznek, L. Cormio, G. Carrieri ................................. 183

Radical prostate cancer treatment in the elderly: role of cryotherapy
G. Silecchia, O. Selvaggio, G. Stallone, F. Lugnani, A. Hoznek, G. Carrieri ........................... 189

Robot-assisted pelvic lymphadenectomy for prostate cancer.
Potentially advantageous in the elderly?
M. Di Nauta, L. Cormio, R. Villani, V. Mancini, É. Barret, G. Carrieri .............................. 195

Multiparametric magnetic resonance imaging/transrectal ultrasound fusion-guided prostate biopsy: a comparison with systematic transrectal ultrasound-guided prostate biopsy
G. Silecchia, U. Falagario, F. Sanguedolce, L. Macarini, R. Autorino, L. Cormio ................. 200

Prostate cancer detection rate of multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy. Impact of clinical indications on biopsy outcome
G. Silecchia, O. Selvaggio, P. Milillo, A. Tewari, G. Stallone, G. Carrieri ............................. 205

A lycopene and olives vegetation water compound improves lower urinary tract symptoms in men with histologically-proven benign prostatic hyperplasia and inflammation
G. Silecchia, O. Selvaggio, E. Barret, F. Sanguedolce, G. Stallone, L. Cormio ................. 211

www.jgerontology-geriatrics.com
Hemostatic sealant in tubeless percutaneous nephrolithotomy: a monocentric experience
M. Auciello, A. Mangiatordi, G. Stallone, G. Carrieri, A. Hoznek, L. Cormio ............ 216

Reviews
Micropapillary bladder cancer, a variant histology of the elderly
F. Sanguedolce, A. Cormio, B. Calò, M. Landriscina,
E. Carvalho-Dias, L. Cormio ................................................................. 222

Role of age in prostate and bladder cancer. A critical overview
F. Sanguedolce, M. Chirico, G. Stallone, L. Cindolo, A. Tewari, G. Carrieri .......... 228

Nephrolithiasis in the elderly
A. Carella, S. Leo, B. Infante, A. Hoznek, G. Grandaliano, G. Stallone ............... 233

Molecular markers predicting disease outcome in bladder cancer. Should we shift from the classical cell-cycle regulators to HER2 oncogene?
F. Sanguedolce, A. Cormio, B. Calò, N. Buffi, R. Autorino, L. Cormio ............... 239

Lower urinary tract symptoms in elderly men: a simple yet comprehensive approach
V. Mancini, M. Balzarro, E. Illiano, A. Hoznek, G. Stallone, G. Carrieri ............ 245

Unmet clinical questions in elderly patients with locally advanced and metastatic bladder cancer
G. Pezzicoli, A. Ummarino, F. Maddalena, R. Villani,
E. Barret, M. Landriscina ................................................................. 253

Age, mitochondria and bladder cancer
A. Cormio, C. Musicco, V. Pesce, R. Villani, A. Antonelli, E. Barret .................... 260

Clinical Observations in Geriatrics
Radical cystectomy and orthotopic neobladder in fit octogenarians
B. Calò, E. Carvalho-Dias, R. Autorino .................................................. 265
Elderly patients and prostate biopsy. How old is too old?

U.G. Falagario1, Sanguedolce2, G. Stallone3, N. D’Altilia1, A. Tewari4, G. Carrieri1

1 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 2 Section of Pathological Anatomy, Department of Clinical and Experimental Medicine, University of Foggia, Italy; 3 Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 4 Department of Urology, Mount Sinai School of Medicine, New York, USA

INTRODUCTION

Prostate cancer (PCA) is the most common malignancy in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed. The median age at diagnosis is 66 years, and although many elderly men who are diagnosed with PCA will die from other causes, 70% of deaths occur in men older than 75 years. Since incidence and mortality rise steeply with age, the PCA burden is expected to increase with exponential aging of the population.

Other potential explanations for increasing PCA incidence stay in the increased use of PSA testing, novel imaging techniques and biomarkers. Given the risk of overdiagnosis turning into overtreatment, the role of PSA testing in the elderly is a matter of debate. The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older. The International Society of Geriatric Oncology (SIGO) guidelines for the management of elderly PCA patients outlines the risks of both over- and under-treatment and the importance of assessing overall health status, comorbidities, and cognitive function.

Background & aims. Based on autopsy findings that many elderly men bear clinically-insignificant PCA, physicians tend to be reluctant to advise PSA testing in men > 75 years and to recommend prostate biopsy, particularly in men who suffer from lower urinary tract symptoms. Herein, we compared the outcome of prostate biopsy in men ≤ 75 and > 75 years to determine whether such procedure is worth in the elderly patient.

Methods. We assessed the rates of prostate cancer and of clinically-significant prostate cancer in men ≤ 75 and > 75 years who underwent prostate biopsy at our Institution. We also assessed prostate volume, peak flow rate, post-void residual and International Prostate Symptoms Score.

Results. Of 3350 with PSA up to 20 ng/ml, 387 (11.5%) were > 75 years. They had higher PSA, similar prostate volume, lower Peak Flow rate and International Prostate Symptoms Score and higher post-void residual than their younger counterpart. Prostate cancer detection rate was 62%, as opposed to 43% in their younger counterpart (p < 0.0001); clinically-significant prostate cancer rate was 42.9% as opposed to 24% (p < 0.0001). Findings were almost the same in the 2740 patients with PSA up to 10 ng/ml. Multivariate analysis pointed out that all clinical variables independently predicted clinically-significant prostate cancer but elderly patients with PSA up to 10 ng/ml had an almost 5-fold greater risk of such diagnosis than their younger counterpart.

Conclusions. Given their risk of harboring clinically-significant prostate cancer, elderly patients with rising PSA deserve prostate biopsy as early detection may provide significant benefits in terms of disease-free and overall survival.

Key words: Elderly, Prostate cancer, Prostate biopsy, High grade prostate cancer, PSA screening, Early diagnosis
in personalizing management. Having said this, they conclude that age alone should not preclude initial screening and, in case of a cancer diagnosis, effective treatment. Somewhere in between is the position of current EAU guidelines that recommend to stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit. This position is likely due to the perception of most PCas in the elderly being clinically insignificant, perception supported by the observation of increasing incidence of PCAs with aging at autopsy.

In this scenario, physicians tend to be reluctant to advise PSA testing in men > 75y as well as to recommend prostate biopsy (PBx) for increased PSA levels; this is even more true for those with PSA in the grey zone (4-10 ng/ml) who suffer from lower urinary tract symptoms (LUTS).

In the present study we compared the outcome of PBx driven by increased PSA and/or abnormal DRE men ≤ 75 and > 75y to determine whether such procedure is worth in the elderly patient.

PATIENTS AND METHODS

Data of patients scheduled for ultrasound-guided transrectal PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database. All patients underwent PSA measurement before DRE and transrectal ultrasound (TRUS). Uroflowmetry (UFM) was carried out before PBx, waiting for the patient to report a strong sensation to void. Following local non-infiltrative anesthesia, TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme. Following the procedure Serenoa Repens was given as needed.

Men with PSA > 20 ng/ml, men receiving 5 alfa-reductase inhibitors (5-ARIs), or who had previously undergone invasive treatment for benign prostatic hyperplasia, or with dwelling urethral catheters were excluded from the present study.

A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate, and PCa. We compared the rates of all PCAs and of clinically significant PCAs (CSPCa), defined as those with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus in men ≤ 75 and > 75y. Data were further stratified according to pre-biopsy PSA levels.

STATISTICAL ANALYSIS

Continuous variables are reported as medians and interquartile range and analyzed by the Kruskal Wallis test. Categorical variables are reported as frequencies and analysed by the Chi square Test. Multivariate logistic regression analysis was carried out to determine independent predictors of CSPCa. Statistical Analyses were performed using STATA 14 (StataCorp LP, College Station, TX, USA). Significance was set at α = 0.05.

RESULTS

Between January 2006 and July 2018, a total of 3820 patients underwent TRUS-guided PBx at our Institution; 3350 met the inclusion criteria. Their clinical characteristics and pathology findings are shown in Table I. A total of 387 patients (11.5%) were > 75 years and about 18% of them were > 80 years old. Elderly men had higher PSA and higher rates of suspicious DRE than their younger counterpart. As for benign prostatic obstruction (BPO)-related parameters, elderly patients had similar prostate volume (PVol), lower Peak Flow rate (PFR) and International Prostate Symptoms Score (IPSS) and higher post-void residual (PVR) than their younger counterpart.

Most important, cancer detection rate (CDR) was significantly higher in elderly men than in the younger ones (62.01 vs 43%, respectively; p < 0.0001); the same applied to CSPCa (42.9 vs 23.6%, respectively; p < 0.0001).

In the sub-analysis of the 2740 patients with PSA up to 10 ng/ml (Tab. II), findings remain the same, as elderly men had higher PSA, higher rates of suspicious DRE, similar PVol, lower PFR and IPSS) and higher PVR than their younger counterpart. Again, cancer detection rate (CDR) was significantly higher in elderly men than in the younger ones (62 vs 39%, respectively; p < 0.0001) and the same applied to CSPCa (40 vs 21%, respectively; p < 0.0001). Multivariate analysis pointed out that all clinical variables independently predicted CSPCa, but age was associated with the greater risk. Specifically, elderly patients had a 4.14-fold greater risk of being diagnosed with CSPCa then their younger counterpart and such risk raised to 4.96 in patients with PSA up to 10 ng/ml (Tab. III).

DISCUSSION

The present study pointed out that, in spite of their BPO-related parameters, elderly patients had a
significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCas, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterpart. Interestingly, and somehow confuting the assumption that elderly patients tend to harbor clinically-insignificant PCAs, elderly men had a significantly higher risk of being diagnosed with PCa than their younger counterp...
similar rate of low-risk ISUP 1 cancers but a significantly higher rate of CSPCAs than their younger counterpart. A novel nomogram based on BPO-related parameters (PFR, PVol, PVR) has recently been shown to predict the risk of prostate cancer at first prostate biopsy with a model predictive accuracy of 0.768 for overall PCAs and of 0.8002 for Clinical significant PCAs 19. Question remains whether such clinical factors may impact on treatment outcome, like smoke in bladder cancer 20. Our findings are consistent with those in literature. Akman et al. 21 analyzed 103 PBxs performed in men aged 75 or more and found that Gleason scores ≥ 7 in 85% and ≥ 8 in 64% of patients. In a larger series of 1446 PBxs, men aged ≥ 75y and with mean serum PSA of 10.4 ng/mL, PCa detection rate was 53%; as much as 78% of these cancers were defined as clinically significant 22. The increased risk of elderly people harboring aggressive PCAs was confirmed also by radical prostatectomy series whereby nearly 90% of men aged > 70y were diagnosed with Gleason score ≥ 7; moreover, they had a significant greater failure rate compared than their matched younger counterpart 23. The latter finding of elderly people having worse outcome was confirmed also in a large cohort of 12,081 men who underwent active treatment; those ≥ 70y had worse outcomes in terms of biochemical recurrence-free survival as well as cancer specific and overall survival 24. An interesting finding of our study was that, among tested clinical variables, age was the most significant predictor of harboring CSPCAs. It was quite striking that such evidence was even stronger in men with PSA up to 10 ng/ml, who had an almost 5-fold greater risk of being diagnosed with CSPCAs than their younger counterpart. Such finding strongly question the assumption that in elderly men with LUTS, a PSA in the grey zone (4-10 ng/ml) in unlikely to be related to the presence of PCAs. The main question however remains whether elderly patients would benefit from an early diagnosis of PCa. Gulati et al. 25 developed 3 models of PCa natural history to project risks of clinical progression events and disease-specific deaths for PSA-detected cases assuming they receive no primary treatment. Among men with PSA detected Gleason score 8-10 disease, the three models project that 29-43% would die of their disease by 10 years after PSA detection in absence of treatment. Of course, question remains regarding the ideal treatment option in such patients. While radical prostatectomy remains the most efficient treatment option, voiding complications remain a key issue though such complication, like for several other surgical procedures, is linked to case volume 26 27. In conclusion, given their significant risk of harboring PCa and CSPCAs, elderly patients with LUTS and rising PSA deserve PBx even when their PSA is just in the grey zone (within 10 ng/ml) and even if their life expectancy is less than 10 years. Evidence suggest that early diagnosis and treatment of clinically significant aggressive PCAs may provide significant benefits in terms of disease-free survival and overall survival. Therefore, like for other common benign urological conditions, the final clinical decision has to rely on wise clinical judgment 29 30.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**

Elderly patients and prostate biopsy. How old is too old?


Ko J, Falzarano SM, Walker E, et al. Prostate cancer patients older than 70 years treated by radical prostatectomy have higher biochemical recurrence rate than their matched younger counterpart. Prostate 2013;73:897-903.


Background and aims. The impact of age on urinary continence recovery after retropubic radical prostatectomy is debated. We tested the impact of age on urinary continence after RRP by comparing 3 age groups, namely < 60 years, 60 to 70 years, and > 70 years.

Methods. From our prospectively-maintained database on retropubic radical prostatectomy (RRP), we identified patients aging < 60 (Group 1), 60-70 (Group 2) and > 70 years (Group 3). Postoperatively, all patients were referred to our continence nurses who assessed them by 24-h pad test and the International Consultation Incontinence Questionnaire (ICIQ-short form) at one week, then monthly for the first year, and then biannually. Patients with a 24-h pad test ≤ 20gr were considered continent.

Results. A total of 498 patients met the inclusion criteria, 108 in Group 1, 263 in Group 2 and 127 in Group 3. Continence recovery rate progressively increased over time in all groups. In spite of Group 3 having a trend towards a lower continence rate, differences among groups were not statistically significant. Interestingly, multivariate analysis pointed out that, in spite of elderly patients having greater prostate volume and lower rate of nerve-sparing procedures, no factor including age significantly predicted continence recovery.

Conclusions. Continence recovery after retropubic radical prostatectomy is a complex phenomenon. The present study pointed out that, after having taken into account potentially relevant tested variables, elderly patients were not at higher risk of urinary incontinence after this procedure.

Key words: Urinary incontinence, Radical prostatectomy, Elderly, Nerve-sparing surgery
Elderly patients are not at higher risk of urinary incontinence after radical prostatectomy

retropubic radical prostatectomy (RRP), but data supporting functional advantages are still lacking. Urinary continence is intensely related to patient’s quality of life and it is important to differentiate among those men who need pads for their leak from those who do not but maybe use just one of it for safety. Indeed, large multicenter studies pointed out that following RRP 1% to 40% of patients complain of persistent urinary incontinence; this wide range of incidence depends on the definition of urinary incontinence, the evaluating tools, and the length of follow-up. Another relevant issue is represented by the identification of risk factors for leakage. Several factors, including age, stage of PCa, preoperative continence status, obesity, surgical technique (nerve sparing, bladder neck preservation, posterior reconstruction of Denovilliers’ musculo-fascial plate, anterior periurethral suspension suture, length of residual membranous urethra) have been suggested to potentially play a role. Age may impact not only on occurrence of incontinence but also on its overall burden, particularly in elderly with several other comorbidities. The present study aimed to determine the impact of age on urinary continence after RRP by comparing 3 age groups, namely < 60 years, 60 to 70 years, and > 70 years.

PATIENTS AND METHODS

Data of patients scheduled for RRP at our institution between February 2009 to October 2017 were entered into our prospectively maintained, Internal Review Board approved database. Men were divided in 3 groups according to age: group 1 = age < 60y, group 2 = age between 60y and 70y, and group 3 = age > 70y. To avoid potential inclusion biases, we elected to analyze only those patients who had undergone prostate biopsy (PBx) at our institution. All patients underwent uroflowmetry (UFM) before PBx unless they had an indwelling urethral catheter. PBx was carried out under local non-infiltrative anesthesia. TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 12-core biopsy scheme. All patients received RRP as described by Walsh and standardized at our Institution. The indication for a nerve-sparing procedure was based on patient’s International Index of Erectile Function-5 and local extent of the disease, while the indication for (posterior and anterior) reconstruction was based on the assigned Consultant (GC: no reconstruction and LC reconstruction). A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate, and PCa. Clinically significant PCa was defined in cancer with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus.

All patients were referred to our specialist nurses for pelvic floor muscle exercises; they who saw them 1 week after discharge, then monthly for the first year, and then biannually. Urinary continence follow-up included the International Consultation Incontinence Questionnaire-short form (ICIQ-short form) and the 24-hour pad-test. Patients leaking up to 20 gr in 24 hours were defined as continent. Patients lost at follow-up or with incomplete data were excluded.

RESULTS

A total of 498 patients met the inclusion criteria. Baseline characteristics of the three populations are shown in Table I. As for benign prostatic obstruction (BPO) parameters, there was no difference between groups inpeak flow rate (PFR) and post-void residual (PVR) but prostate volume (PVol) significantly increased with age. There was no difference in GGG at PBx, in pelvic lymph node dissection (PLND) rate and in reconstruction rate, whereas the nerve-sparing procedure rate significantly decreased with age (Tab. I). Table II shows that continence rate increased over time in all 3 groups. In spite of a trend towards a lower continence rate in the elderly group, the difference in continence rate among the 3 groups at 1, 6 and 12 months follow-up did not reach statistical significance. Specifically, the 12 months continence rate reached 81.5, 81.4 and 76.4% in group 1, 2, and 3 respectively (p = 0.5). The ICIQ score decreased over time in all 3 groups; again, in spite of a trend towards a higher ICIQ score in the elderly group, differences among the 3 groups at 1, 6 and 12 months follow-up did not reach statistical significance (Tab. II).

Finally, multivariate analysis pointed out that age, prostate volume and nerve-sparing procedure did not predict continence recovery after RRP (Tab. III).
Of the 99 patients who remained incontinent, only 24 elected to undergo surgical treatment. The 14 with mild/moderate incontinence received Pro-Act® adjustable balloons periurethral implants; 4 patients were < 60 years, 5 were 60 to 70 years, and 5 were > 70 years. The other 10 with moderate/severe incontinence received a Zephir ZSI 375® artificial sphincter implant; 5 patients were < 60 years, 1 was 60 to 70 years, and 4 were > 70 years.

**DISCUSSION**

The present study pointed out that, in spite of a trend towards a lower continence rate in elderly patients undergoing RRP, the difference in continence rate and ICIQ scores among the 3 age groups was not statistical significant. Indeed, multivariable analysis pointed out that age, prostate volume and nerve-sparing procedure did not predict continence recovery after RRP.

The predictive value of age is controversial. A large study by Nilsson et al. recently pointed out that age at surgery predicted the long term risk for urinary incontinence, with an estimated relative increase of 6% per year; in addition to age as a risk factor, educational level also impacted incontinence, with low educational level, being associated with a 2.5 times risk of incontinence. Similarly, Stanford et al. demonstrated that urinary control and sexual function after RRP varied according to age since 13.8% of men aged 75-79 vs 0.7-3.6% of

Table I. Patients characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt; 60y) (n = 108)</th>
<th>Group 2 (60-70y) (n = 263)</th>
<th>Group 3 (&gt; 70y) (n = 127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume, mL</td>
<td>40 (28.50)</td>
<td>45 (35.60)</td>
<td>46 (33.61)</td>
<td>0.009</td>
</tr>
<tr>
<td>PFR, mL/sec</td>
<td>13.50 (8.50-17.90)</td>
<td>13.90 (10.20-19.00)</td>
<td>12.20 (9.00-16.90)</td>
<td>0.2</td>
</tr>
<tr>
<td>PVR (ml)</td>
<td>20.00 (0.00-45.00)</td>
<td>20.00 (0.00-50.00)</td>
<td>25.00 (0.00-50.00)</td>
<td>0.8</td>
</tr>
<tr>
<td>GGG, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>42 (60.9%)</td>
<td>94 (54.3%)</td>
<td>38 (49.4%)</td>
<td>0.7</td>
</tr>
<tr>
<td>-2</td>
<td>11 (15.9%)</td>
<td>27 (15.6%)</td>
<td>10 (13%)</td>
<td></td>
</tr>
<tr>
<td>-3</td>
<td>4 (5.8%)</td>
<td>11 (6.4%)</td>
<td>5 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td>11 (15.9%)</td>
<td>31 (17.9%)</td>
<td>17 (22.1%)</td>
<td></td>
</tr>
<tr>
<td>-5</td>
<td>1 (1.4%)</td>
<td>10 (5.8%)</td>
<td>7 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>NS procedure, n (%)</td>
<td>58 (66.7%)</td>
<td>75 (34.7%)</td>
<td>16 (15.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PLND, n (%)</td>
<td>61 (70.1%)</td>
<td>140 (63.9%)</td>
<td>73 (70.9%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Reconstruction, n (%)</td>
<td>57 (52.8%)</td>
<td>113 (43.0%)</td>
<td>64 (50.4%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Data are expressed as median (95% confidence interval). GGG: Gleason Grade Group; NS: nerve sparing; PLND: pelvic lymph node dissection.

Table II. Urinary Continence outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (&lt; 60y) (n = 108)</th>
<th>Group 2 (60-70y) (n = 263)</th>
<th>Group 3 (&gt; 70y) (n = 127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pad&gt;20 gr, n (%)</td>
<td>57 (52.8%)</td>
<td>133 (50.6%)</td>
<td>61 (48.0%)</td>
<td>0.8</td>
</tr>
<tr>
<td>ICIQ score</td>
<td>8.6 ± 8.7 (7.0-10.3)</td>
<td>9.24 ± 8.5 (8.3-10.3)</td>
<td>9.4 ± 8.4 (8.0-10.9)</td>
<td>0.7</td>
</tr>
<tr>
<td>1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pad&gt;20 gr, n (%)</td>
<td>64 (59.3%)</td>
<td>152 (57.8%)</td>
<td>66 (52.0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>ICIQ score</td>
<td>6.5 ± 7.6 (5.5-8.5)</td>
<td>7.4 ± 7.9 (6.3-8.2)</td>
<td>8.07 ± 8 (6.7-9.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pad&gt;20 gr, n (%)</td>
<td>81 (75.0%)</td>
<td>203 (77.2%)</td>
<td>90 (70.9%)</td>
<td>0.4</td>
</tr>
<tr>
<td>ICIQ score</td>
<td>3.5 ± 5.9 (2.4-4.7)</td>
<td>3.6 ± 6.3 (2.8-4.3)</td>
<td>4.7 ± 8 (3.5-6.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pad&gt;20 gr, n (%)</td>
<td>88 (81.5%)</td>
<td>214 (81.4%)</td>
<td>97 (76.4%)</td>
<td>0.5</td>
</tr>
<tr>
<td>ICIQ score</td>
<td>2.5 ± 5.3 (1.5-3.5)</td>
<td>3.0 ± 5.9 (2.3-3.7)</td>
<td>3.85 ± 6.63 (2.6-4.9)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Data are express as means ± standard deviation (95% Confidence interval); ICIQ: International Consultation Incontinence Questionnaire-short form (ICIQ-short form)
Elderly patients are not at higher risk of urinary incontinence after radical prostatectomy

Younger ones had high level of urinary incontinence at 18 months follow-up. Eastham et al. 23 assessed the rate of urinary continence at two years follow-up in a population of 581 patients concluding that preoperative urinary disorders, nerve-sparing procedure, clinical tumor stage, age of patient and type of vesico-urethral anastomosis are the most negative important factors on urinary continence. Finally, in a large series of 985 RRP 7, men aged > 65 years had a higher probability of incontinence compared with their younger counterpart, with a significant worsening in non nerve-sparing procedures.

On the other hand, Kundu et al. 24 pointed out, in a series of 3477 patients, that nerve-sparing procedure did not influence the recovery of continence. Most important, Steiner et al. 25 investigated age, prostate volume, prior transurethral resection of the prostate, pathological stage and preservation or wide excision of the neurovascular bundles, and they found no correlation with urinary continence, but only 21 of the 593 patients were ≥ 70 y. Catalona et al. 26 pointed out that continence recovery occurred in 409 of 435 patients (94%) and did not correlate with patient age, tumor stage or nerve sparing surgery.

Another study linked elderly age and number of comorbidities to a negative influence on continence recovery during the first year after RRP 27. Our study showed no difference in time to continence recovery in the 3 age groups.

The exact mechanisms of post-RRP urinary incontinence in not completely clear. Urinary continence is dependent on the integrity of the internal urethral sphincter (IUS) and/or external urethral sphincter (EUS), as well as prostate support structures, including muscles and fascias. Following gland removal, continence seems to rely mainly on EUS. Age-related sphincteric modifications are generally responsible for a progressive reduction in striated muscle cells 3 7. Having said this, our study showed a trend towards a lower continence rate in the elderly patients, but findings were not statistically significant. While this may partly be due to elderly patients having larger prostates and lower rate of nerve-sparing procedure, both potentially negative factors, multivariate analysis pointed out that no clinical variable predicted continence rate. This finding would somehow suggest that the main determinant of continence recovery remains a proper surgical technique causing the less damage to EUS. Indeed, experience with robot-assisted radical prostatectomy has shown that even some surgical clips may result in continence problems 28. Like for other surgical procedures, small technical details may play a relevant role in final outcome 29-31. Not to mention the potential role of systematically training patients in pelvic floor exercises during follow-up.

Potential study limitations include the relatively small number of elderly patients, but this is not much different from other available studies, and some heterogeneity in patients clinical features, but this reflects well everyday clinical practice.

In conclusion, elderly patients seem to obtain similar results, in terms of urinary continence recovery after RRP, than their younger counterpart providing careful anatomical dissection and strict urinary continence follow-up. In view of this, elderly should not be considered at higher risk of urinary incontinence after RRP.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


Is percutaneous nephrolithotomy effective and safe in elderly patients? Outcomes of a case-control study

A. Mangiatordi¹, M. Auciello¹, G. Stallone², A. Saita³, A. Hoznek⁴, L. Cormio¹

¹ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ³ Urology, Humanitas Clinical and Research Hospital, Rozzano, Milan, Italy; ⁴ Department of Urology, Henri Mondor Hospital, Créteil, France

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the recommended treatment option for large or otherwise complex renal or proximal ureteral stones. The procedure involves creating a narrow percutaneous access to the kidney and the formation of a working tract connecting the flank surface with the intrarenal collecting system through which nephroscopy is performed. This allows endoscopic stone disintegration and removal of the stone fragments. Though effective, this procedure is considered challenging as serious and even lethal complications may occur. Most life-threatening situations are due to postoperative infection, systemic inflammatory response syndrome (SIRS) and sepsis.¹ ² Even if the age itself is not considered a contraindication to PCNL, decreased functional reserve, comorbid conditions, and the reduced efficiency of the immune system associated with aging can increase the risk of complications.

Background and aims. Percutaneous nephrolithotomy is the recommended treatment option for large or otherwise complex renal or proximal ureteral stones. Being a challenging procedure, its efficacy and safety in elderly patients is questioned. The present study aimed to determine the impact of age on percutaneous nephrolithotomy outcome, comparing patients < 70y with those ≥ 70y.

Methods. We analysed our prospectively maintained Internal Review Board approved database on percutaneous nephrolithotomy to compare demographics, perioperative outcomes and postoperative complications of patients < 70y with those ≥ 70y.

Result. Among 638 patients treated between April 2005 and March 2018, 553 were < 70y and 85 were ≥ 70y. There was no difference between the two populations in all preoperative characteristics but American Society of Anaesthesiologists score, which was significantly worse in elderly patients. Operative outcomes were similar in the 2 populations but elderly patients had a greater complications rate (54.1% vs 42%; p = 0.005) and a higher rate (9.4% vs 4.2%; p = 0.0525) of infective complications. Indeed, multivariate analysis showed that age > 70y and positive stone culture were associated with a significantly higher rate of clinically-significant complications.

Conclusions. Percutaneous nephrolithotomy proved to be effective in consecutive/unselected elderly (≥ 70y) candidates to such procedure but at the price of a greater risk of, mainly minor, complications. The higher incidence of infective complications speaks for potentially reduced immune response of such patients and sets the rationale for further addressing this issue.

Key words: PCNL, Percutaneous nephrolithotomy, Elderly, Urolithiasis
A. Mangiatordi et al.  

system, also known as immunosenescence 4, may expose to a greater risk of complications, thereby influencing the surgeon's decision-making process. On the other hand, the incidence of nephrolithiasis in elderly people is growing; because of the high risk of urinary tract infection and renal dysfunction with untreated large kidney stones, a conservative approach may not always be wise 5 6.

To date, a few studies addressed the issue of PCNL efficacy and safety in the elderly. Moreover, quite different age cut-offs, ranging from 60 to 80 years, have been used to define elderly patients. The present study aimed to determine the impact of age on PCNL outcome, comparing patients < 70y with those ≥ 70y.

MATERIAL AND METHODS

Data of patients scheduled for PCNL at our Department were prospectively entered into our Internal Review Board approved dedicated database.

Preoperatively, all patients underwent abdominal computed tomography scanning and urine culture. Antibiotic prophylaxis was carried out according to current recommendations 7. All procedures were carried out in our supine antero-lateral position or in the Galdakao-modified supine position 8-10. Until the end of 2014, standard anesthesia was general whereas, from the beginning of 2015, it was spinal. Renal collecting system was punctured under fluoroscopic guidance using an 18G needle. The percutaneous tract was dilated to 17.5F (mini-PCNL) or to 26-30F (standard PCNL). Following stone/s fragmentation/extraction, flexible ureteroscopy and/or nephroscopy was carried out to check for stone clearance. Whenever possible, the procedure was closed placing a mono-J ureteral stent and a Foley catheter, thus were tubeless or Tachosil-sealed tubeless procedures 11 12. Whenever deemed necessary, we used a double-J stent instead of the mono-J ureteral catheter or a nephrostomy tube 13. All procedures were carried out by one of us (LC).

All patients underwent abdomen X-ray and renal ultrasound (US) at 1 month postoperatively to assess stone free rate (SFR). Abdominal CT was used as needed. Patients with residual fragments ≤ 4mm were considered stone-free 14. Perioperative complications were assessed using the Clavien classification system adjusted for PCNL 2. Infective complications were defined fever or SIRS lasting > 24h, and/or infection.

STATISTICAL ANALYSIS

The Mann-Whitney U-test was used for continuous variables, whereas the Chi-square test was used for categorical variables. Univariate and multivariate analysis were used to test the impact of clinical factors on complications Clavien > 1. Data were analysed by Stata 14 (StataCorp LP, College Station, TX, USA). All tests were 2-sided with a significance level set at p < 0.05.

RESULTS

A total of 638 patients treated between April 2005 and March 2018 were eligible for the present study; of them, 553 (86.7%) were < 70y and 85 (13.3%) were ≥ 70y. Their descriptive characteristics are reported in Table I. There was no difference between the two populations in most baseline characteristics, specifically gender, body mass index (BMI), positive preoperative urine culture and stone size. However, as expected, elderly patients had a significantly greater ASA score due to their comorbidities. Specifically, elderly patients were more likely to have cardiovascular comorbidities, worsened renal function, and to be on anticoagulant and antiplatelet therapy. Elderly patients were more likely to have spinal anesthesia; otherwise, there was no difference in the operative characteristics of the two populations, including Amplatz sheath size, operative time, tubeless procedure and positive stone culture rates (Tab. I).

Table II reports outcomes in the two populations. There was no difference in median Hb loss, blood transfusion rate and SFR. Elderly patients had an overall greater complication rate (54.1 vs 42%, respectively; p = 0.005) and longer postoperative hospital stay. However, most complications were minor (Clavien 1) and there was a difference between the two populations for Clavien grade 3 complications due to the higher rate of infective complications (9.4 vs 4.2%, respectively) seen in elderly patients.

Finally, Table III reports univariate and multivariate analyses of factors predicting complications Clavien > 1. Univariate analysis showed that age > 70y, operative time, and positive stone culture rates were associated with a significantly higher risk of Clavien > 1 complications. At multivariate analysis however only age > 70y and positive stone culture confirmed to be significant predictors of Clavien > 1 complications.

DISCUSSION

The present study pointed out that elderly patients suffered more complications than their younger counterpart in spite of the two populations being similar for most preoperative, operative and also postoperative outcomes. Indeed, there was a significant difference in infective complications, which was likely due to the
Is percutaneous nephrolithotomy effective and safe in elderly patients? Outcomes of a case-control study

Fulop et al. 15 reported that frailty in elderly people is an evolving concept defining a complex phenomenon that leads to dysregulation of several physiological systems, including the neuroendocrine, metabolic and immune inflammatory system. The latter determines how an organism is able to face different extrinsic and intrinsic challenges. Age-related changes of the immune system are defined as ‘immunosenescence’ and involve alterations in both the innate and adaptive immune systems that lead to a disequilibrium of the immune response resulting in low-grade efficacy 16 17. As a consequence, elderly people are more susceptible to infections, cancers and autoimmune disorders. Though several attempts have been made to create algorithms and strategies that can assess frailty syndrome, an universally accepted definition still lacks.

The correlation between age and infective complications was further supported by multivariate analysis showing that age > 70y and positive stone culture were significant predictors of Clavien > 1 complications, including infective complications. Again, these findings

**Table I. Patients preoperative and operative characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 70 years (n = 553)</th>
<th>&gt; 70 years (n = 85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>52.0 (41.5, 59.8)</td>
<td>74.4 (72.0, 77.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>300 (54.2%)</td>
<td>42 (49.4%)</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI*</td>
<td>26.0 (24.0, 30.0)</td>
<td>26.1 (24.5, 29.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Positive preoperative urine culture, n (%)</td>
<td>56 (10.1%)</td>
<td>12 (13.6%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Stone size* (mm)</td>
<td>23.0 (18.0, 30.0)</td>
<td>25.0 (18.0, 30.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stone features, n (%)</td>
<td>274 (49.5%)</td>
<td>45 (62.9%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Single</td>
<td>179 (32.4%)</td>
<td>26 (30.6%)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>100 (18.1%)</td>
<td>14 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>ASA score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58 (10.5%)</td>
<td>5 (5.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>448 (81.0%)</td>
<td>62 (72.9%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46 (8.3%)</td>
<td>18 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>General Anesthesia, n (%)</td>
<td>275 (49.7%)</td>
<td>33 (38.8%)</td>
<td>0.06</td>
</tr>
<tr>
<td>“Mini” Amplatz sheath, n (%)</td>
<td>275 (49.7%)</td>
<td>49 (57.6%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Surgical time*, min</td>
<td>75.0 (60.0, 100.0)</td>
<td>75.0 (60.0, 100.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Tubeless, n (%)</td>
<td>424 (76.6%)</td>
<td>70 (82.4%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive stone culture, n (%)</td>
<td>46 (13.0%)</td>
<td>11 (19.0%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Data expressed as medians (interquartile range).

**Table II. Outcome data.**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 70 years (n = 553)</th>
<th>&gt; 70 years (n = 85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective complications, n (%)</td>
<td>23 (4.2%)</td>
<td>8 (9.4%)</td>
<td>0.0525</td>
</tr>
<tr>
<td>HB loss* (g/dl)</td>
<td>1.00 (0.00-2.10)</td>
<td>0.90 (-0.10-2.00)</td>
<td>0.5</td>
</tr>
<tr>
<td>Blood Transfusion, n (%)</td>
<td>25 (5%)</td>
<td>6 (7%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Clavien, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>321 (58.0%)</td>
<td>39 (45.9%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>160 (28.9%)</td>
<td>25 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37 (6.7%)</td>
<td>7 (8.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td>3</td>
<td>31 (5.6%)</td>
<td>11 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (0.7%)</td>
<td>2 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 (0.0%)</td>
<td>1 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Post-operative hospital stay* (days),</td>
<td>3.0 (2.0, 4.0)</td>
<td>3.0 (2.0, 5.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>Stone free, n (%)</td>
<td>392 (71.9%)</td>
<td>63 (75.0%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Data expressed as medians (interquartile range).
would provide further evidence for a less efficient immune system in our elderly population. Though such hypothesis could be supported by the elderly having greater ASA scores, no specific frailty or immunity assessment was made.

Our data are not that different from those reported in literature. Sahin et al.\textsuperscript{18} compared data of 28 PCNL performed in patients > 60y with those of 178 procedures performed in patients ≤ 60y. Though elderly people had a significantly higher incidence of solitary kidney, outcomes in the 2 populations were reported to be similar. Elderly patients however had a greater rate (14 vs 10%) of fever without bacteremia.

Okeke et al.\textsuperscript{19} analysed data of the PCNL Global Study conducted by the Clinical Research Office of the Endourological Society (CROES) to assess the impact of age on PCNL outcome. In this prospective observational study collecting data of 5803 patients treated at 96 centers worldwide between November 2007 and December 2009, elderly (≥ 70y) patients were found to have, in a matched analysis, a statistically significant higher rate of overall complications. Morganstern et al.\textsuperscript{20} retrospectively reviewed perioperative data of octogenarians who underwent PCNL at a high-volume stone center (36 renal units) and matched them to patients < 65 years of age by stone burden and sex (72 renal units). Though octogenarians had a higher mean ASA score, more comorbidities, and worse renal function, no difference in length of hospital stay or stone free rates were seen. Octogenarians did not experience more minor Clavien (1 e 2) or major Clavien (3a e 4b) complications. The authors concluded that, in spite of risk factors, PCNL can be safely and successfully performed in appropriately selected octogenarians without increased perioperative complications.

A strong point of our study was having included consecutive patients providing their cardiovascular status allowed to undergo PCNL. These are somehow different from the concept of “appropriately-selected” population and somehow explain the large number of patients we included. Case volume is a relevant factor in determining outcome in endourological procedures\textsuperscript{21}.

Limitations include being a retrospective analysis, but data were prospectively collected, and absence of a control group managed by observation or by retrograde intrarenal surgery (RIRS); however, the first would have been unethical in symptomatic patients, the latter would have probably exposed elderly patients to a higher risk of potentially serious infective complications\textsuperscript{22}.

To conclude, PCNL proved to be effective in consecutive/unselected elderly (≥ 70y) candidates to such procedure but, somehow expectedly, to be associated with a higher incidence of infective complications. These data suggest that great attention should be paid to such potentially serious complications, setting the rationale for well-designed prospective studies addressing this issue.

**Acknowledgements**

We are grateful to Prof. Maria Manuela Dota, Mother tongue teacher, for her precious linguistic revision.

---

**Table III. Univariate and multivariate analysis predicting Clavien > 1 complications.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O.R. (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>2.19 (1.26 to 3.80)</td>
<td>0.005</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.06 (0.68 to 1.64)</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI, per unit</td>
<td>0.98 (0.93 to 1.04)</td>
<td>0.56</td>
</tr>
<tr>
<td>Positive preoperative urine culture</td>
<td>1.00 (0.46 to 2.21)</td>
<td>0.98</td>
</tr>
<tr>
<td>Stone size, per unit</td>
<td>1.02 (1.00 to 1.04)</td>
<td>0.36</td>
</tr>
<tr>
<td>Stone features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1.33 (0.80 to 2.19)</td>
<td>0.27</td>
</tr>
<tr>
<td>Staghorn</td>
<td>1.72 (0.96 to 3.04)</td>
<td>0.065</td>
</tr>
<tr>
<td>ASA score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.83 (0.41 to 1.66)</td>
<td>0.594</td>
</tr>
<tr>
<td>3</td>
<td>0.49 (0.17 to 1.41)</td>
<td>0.187</td>
</tr>
<tr>
<td>Spinal Anesthesia</td>
<td>0.54 (0.35 to 0.86)</td>
<td>0.009</td>
</tr>
<tr>
<td>“Mini” Amplatz sheath</td>
<td>0.50 (0.32 to 0.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>Surgical time, per unit</td>
<td>1.01 (1.00 to 1.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tubeless</td>
<td>0.45 (0.28 to 0.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Positive stone culture</td>
<td>3.71 (1.96 to 7.03)</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
</tbody>
</table>
CONFLICT OF INTEREST
The authors declare no conflict of interest.

References
Prostatic inflammation is associated with benign prostatic hyperplasia rather than prostate cancer

U. Falagario¹, O. Selvaggio¹, G. Carrieri¹, E. Barret², F. Sanguedolce³, L. Cormio¹

¹Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ²Department of Urology, Institut Montsouris, Paris, France; ³Section of Pathological Anatomy, Department of Clinical and Experimental Medicine, University of Foggia, Italy

INTRODUCTION

Benign prostatic hyperplasia (BPH) and Prostate cancer (PCa) are chronic diseases with a long period for their development and progression. BPH develops from a simple micronodular hyperplasia to a macroscopic volume enlargement and then to clinical expression. Similarly, PCa evolves through early and late precancerous modifications ¹. The prostate is an immunocompetent organ populated by T and B lymphocytes, macrophages and mast cells. Regulatory T cells (CD-4) are located into the fibromuscular stroma whereas Cytotoxic T cells (CD-8) are more distributed around periglandular area creating the so-called Prostate associated Lymphoid Tissue (PALT). Recent studies pointed out a potential relationship between prostatic inflammation and development and progression of BPH and PCa, but question remains if there is a trend towards one or the other disease ²⁻⁶. The present study aimed to determine the relationship between inflammation grade and aggressiveness, as assessed by the Irani G and A score respectively, and the risk of being diagnosed with prostate cancer.

Background and aims. The relationship between prostatic inflammation, benign prostatic hyperplasia and prostate cancer is controversial. The present study aimed to determine the relationship between grade and aggressiveness of prostatic inflammation and the risk of being diagnosed with prostate cancer.

Methods. Grade and aggressiveness of prostatic inflammation were assessed by Irani G and A scores, respectively, in prostate biopsy specimens of men having undergone this procedure because of increased serum PSA and/or digital rectal examination. We also assessed the correlation between Irani G and A scores and clinical variables related to benign prostatic obstruction.

Results. Of the 1178 eligible patients, 615 (52.2%) were diagnosed with PCa; they were older, had greater PSA, suspicious digital rectal examination and peak flow rate but lower post-void residual urine volume, prostate volume and international prostate symptoms score than those without cancer. High-grade inflammation (Irani G 2-3) was significantly more common in patients with benign prostate than in those with PCa and the same applied to highly aggressive inflammation (Irani A 2-3). Indeed, patients with high-grade inflammation had greater PSA, prostate volume, post-void residual and international prostate symptoms score, suggesting high-grade inflammation to correlate with benign prostatic obstruction. Highly-aggressive inflammation conversely correlated only with prostate volume.

Conclusions. Prostatic inflammation seems to be associated with benign prostatic hyperplasia rather than prostate cancer, with benign prostatic obstruction being strictly linked to the degree of inflammation.

Key words: IRANI score, Prostatic inflammation, Benign prostatic hyperplasia, Prostate cancer
Prostatic inflammation is associated with benign prostatic hyperplasia rather than prostate cancer.

**PATIENTS AND METHODS**

Data of patients scheduled for transrectal ultrasound (TRUS)-guided PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database. All patients underwent PSA measurement before DRE and TRUS. Uroflowmetry (UFM) was carried out before PBx, waiting for the patient to report a strong sensation to void. Following local non-infiltrative anesthesia, TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme. Men with PSA > 20 ng/ml, men receiving 5 alpha-reductase inhibitors (5-ARIs), or who had previously undergone invasive treatment for benign prostatic hyperplasia, or with dwelling urethral catheters were excluded from the present study.

A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate, and PCa. Clinically significant PCas (CSPCa) included those with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus. Prostatic inflammation was assessed using the Irani score. Specifically, the grade (G) of inflammatory infiltrate was scored as 0-no inflammatory cells, 1-scattered inflammatory cells infiltrate within the stroma without lymphoid nodules, 2-nonconfluent lymphoid nodules and 3-large inflammatory areas with confluence of infiltrate. Inflammatory aggressiveness (A) was graded as 0-no contact between inflammatory cells and glandular epithelium, 1-contact between inflammatory cell infiltrate and glandular epithelium, 2-interstitial inflammatory infiltrate associated with a clear but limited (< 25% of the examined material) glandular epithelium disruption, and 3-glandular epithelium disruption on more than 25% of the examined material. Irani G score 0-1 represented low-grade inflammation, whereas G score 2-3 represented high-grade inflammation. Similarly, Irani A 0-1 represented low-aggressiveness inflammation, whereas G score 2-3 represented high-aggressiveness inflammation. Grading did not include the types of inflammatory cells (polymorpho nuclear leukocytes, lymphocytes, monocytes or plasma cells).

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

**Statistical analysis**

Continuous variables were reported as median and interquartile range and compared by the Mann-Whitney U-test. Rates were tested by Fisher’s exact test or chi-square test, as appropriate. Statistical significance was set at p < 0.05. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

**RESULTS**

Patients characteristics are summarized in Table I. Of the 1178 eligible patients, 615 (52.2%) were

---

**Table I. Patients characteristics.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benign (n = 563)</th>
<th>Prostate cancer (n = 615)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>65 (60, 69)</td>
<td>68 (63, 73)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PSA (ng/mL)*</td>
<td>6.07 (4.68, 8.40)</td>
<td>6.45 (4.75, 10.00)</td>
<td>0.008</td>
</tr>
<tr>
<td>Suspicious DRE, n (%)</td>
<td>140 (28.5%)</td>
<td>249 (50.1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Prostate volume (mL)*</td>
<td>61.00 (46.50, 81.00)</td>
<td>45.00 (34.00, 60.00)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PFR (mL/s)*</td>
<td>12.00 (8.80, 16.00)</td>
<td>13.00 (9.10, 18.00)</td>
<td>0.010</td>
</tr>
<tr>
<td>PVR (mL)*</td>
<td>30.00 (1.00, 60.00)</td>
<td>20.00 (1.00, 50.00)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>IPSS*</td>
<td>10 (6, 18)</td>
<td>9 (5, 15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Irani G, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>341 (60.6%)</td>
<td>444 (72.2%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2-3</td>
<td>222 (39.4%)</td>
<td>171 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Irani A, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>427 (75.8%)</td>
<td>541 (88.0%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2-3</td>
<td>136 (24.2%)</td>
<td>74 (12.0%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as medians (interquartile range).
diagnosed with PCa; they were older, had greater PSA, suspicious DRE and peak flow rate (PFR), but lower prostate volume (PVol), post-void residual (PVR) and international prostate symptoms score (IPSS) than those without cancer. Interestingly, high-grade inflammation (Irani G 2-3) was significantly more common in patients with benign prostate than in those with PCa and the same applied to highly aggressive inflammation (Irani A 2-3).

In view of this, we looked at the correlation between Irani scores and BPO-related parameters (Tab. II). Interestingly, patients with high-grade inflammation (Irani G 2-3) had greater PSA, PVol, PVR and IPSS but lower PFR than those with low-grade inflammation; thus a strict correlation with BPO-related parameters. Conversely, highly-aggressive inflammation was associated only with PVol (Tab. III).

Finally, there was no correlation between Irani scores and GGG in patients with PCa.

**DISCUSSION**

The present study pointed out that high-grade inflammation (Irani G 2-3) was significantly more common in patients with BPH than in those with PCa and the same applied to highly-aggressive inflammation (Irani A). A novel finding of our study was that inflammation grade strictly correlated with BPO-related parameters. Specifically, patients with high-grade inflammation had greater PSA, PVol, PVR and IPSS but lower PFR than those with low-grade inflammation.

Our findings are in agreement with those by Nickel et al. who evaluated the relationship between prostatic inflammation, prostate volume and the degree of LUTS. They evaluated 8224 men aged 50-75 years with BPH undergoing prostate biopsy and included in the REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial. Prostatic inflammation, scored as none, mild, moderate, or marked, was found in 77.6% of patients. Patients with chronic inflammation had higher prostate volumes than those without inflammation (46.5 vs 43.4 mL, respectively; p < 0.001) as well as higher IPSS (8.8 vs 8.2, respectively; p < 0.001).

In a cohort study of 282 patients, Robert et al. found a significant association among the degree of prostatic inflammation, prostate volume, and urinary symptoms. Specifically, mean prostate volume was 62 ml in patients with low-grade inflammation and 77 ml in those with high-grade (p = 0.002); similarly, mean IPSS score was 12 and 21 in low-grade and high-grade inflammation (p = 0.02), respectively.

The correlation between prostatic inflammation and serum PSA levels has been highlighted by Irani et al. who concluded that the inflammatory aggressiveness (Irani A), defined as rupture of the prostatic epithelium, was the morphological-diagnostic parameter that correlates most with the rise of the PSA. Accordingly, Song et al. showed that, in patients undergoing surgery for...

<table>
<thead>
<tr>
<th>Table II. Association between Grade of inflammation (Irani G) and patients’ clinical and pathological features.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irani G0-1</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Age (y)</strong>*</td>
</tr>
<tr>
<td><strong>PSA (ng/mL)</strong>*</td>
</tr>
<tr>
<td><strong>Prostate volume (mL)</strong>*</td>
</tr>
<tr>
<td><strong>PFR (mL/s)</strong>*</td>
</tr>
<tr>
<td><strong>PVR (mL)</strong>*</td>
</tr>
<tr>
<td><strong>IPSS</strong>*</td>
</tr>
</tbody>
</table>

*Data are expressed as medians (interquartile range).

<table>
<thead>
<tr>
<th>Table III. Association between aggressiveness of inflammation (Irani A) and patients’ clinical and pathological features.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irani A0-1</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Age (y)</strong>*</td>
</tr>
<tr>
<td><strong>PSA (ng/mL)</strong>*</td>
</tr>
<tr>
<td><strong>Prostate volume (mL)</strong>*</td>
</tr>
<tr>
<td><strong>PFR (mL/s)</strong>*</td>
</tr>
<tr>
<td><strong>PVR (mL)</strong>*</td>
</tr>
<tr>
<td><strong>IPSS</strong>*</td>
</tr>
</tbody>
</table>

*Data are expressed as medians (interquartile range).
BPH, the aggressiveness of inflammatory infiltration was a significant contributor to elevated PSA levels. Thus, patients with BPH with high levels of serum PSA might be considered at higher risk of harbouring chronic inflammation. In clinical practice this leads many patients with BPH and prostatic inflammation to undergo PBx because of increased serum PSA levels. Indeed, we demonstrated that BPO-related parameters were independent predictors of the risk of being diagnosed with PCs; specifically, the more the BPO the less the risk of being diagnosed with PCs. Based on these findings, we developed a novel BPO-related parameters nomogram that may help reducing the number of unnecessary PBxs, thus exposing patient to the risk of overdiagnosis and consequent overtreatment. Another front of research is assessing the role of inflammation in conjunction with novel molecular markers. Recently, Pretxarin 3, a marker potentially related to prostatic inflammation and immune-response has been shown to significantly outperform PSA (AUC 0.92 vs 0.55) in predicting the risk of being diagnosed with PCs; these findings however await validation in a large series of patients scheduled for first PBxs.

Fujita et al. found that increased monocyte chemo-tactic protein-1 (MCP-1) levels in prostatic secretions correlated with prostate volume, and hypothesised that MCP-1 and macrophages might play a role in the development of prostatic inflammation and in the pathogenesis of BPH. An in vitro study by Latil et al. elegantly reported that phytotherapeutic agents, such as the hexanic lipidosterolic extract of Serenoa Repens, inhibit MCP-1 expression by human prostate cells blocking key steps of the inflammation process. More controversial is the relationship between prostatic inflammation and non-steroidal anti-inflammatory drugs (NSAID). While previous studies pointed out a protective association between NSAID use and measures of BPH, more recent ones pointed out a close relationship between NSAID usage and increase in BPH risk and the probability of BPH progression to a stage requiring surgical management.

In conclusion, prostatic inflammation correlates to BPH more than to PCa, with BPO playing a key role. If and how this clinical factor may impact on treatment outcome, like smoke in bladder cancer, remains to be determined. For sure, the role of inflammation and therefore of modulators of the immune response, which are opening new pathways in several urological cancers, deserves attention.

Conflict of Interest
The authors declare no conflict of interest.

References
**Background and aims.** The mechanism of action of intravesical Bacille Calmette-Guerin (BCG) is supposed to be linked to the efficiency of the immune system. Since senesce could negatively affect the immune system efficiency, BCG efficacy in the elderly has been questioned. The present study aimed to determine whether elderly patients (≥ 70y) with high-grade T1 bladder cancer (BC) benefit from adjuvant intravesical instillation of BCG.

**Methods.** Study population consisted of 183 patients (median age 79y); 65 received BCG, both induction and one-year maintenance, and 118 did not. Follow-up consisted of urine cytology and cystoscopy every 3 months for the first two years, every 6 months for the third year, and then yearly. Chest/abdomen computed tomography was performed every year to rule out upper tract or metastatic disease.

**Results.** Mean follow-up was 45 months (range 1-177). Kaplan-Meier plots pointed out that treated patients had significantly better recurrent-free survival (RFS) and progression-free survival (PFS) than the untreated ones. The 40-month cancer-specific survival was 86.2% in treated and 79.7% in untreated patients, but such difference was not statistically significant. Multivariate Cox's proportional hazard regression analysis pointed out that BCG treatment was the only significant independent predictor of RFS and PFS. There was no serious BCG-related adverse reaction; 2 (3.1%) patients suffered moderate flu-like or lower urinary tract symptoms that resolved with symptomatic treatment.

**Conclusions.** Intravesical BCG proved to be safe and beneficial in elderly patients with high-grade T1 BC. Age per se should not be considered a contraindication to such treatment.

**Key words:** BCG, Elderly, Bladder cancer, T1, High grade/G3
an antitumoral effect mediated by the interaction between antigen presenting cells and lymphocytes Th1. This leads to priming of CD8+ cytotoxic T-cells, activation of Natural Killer cells, and release of inflammatory cytokines such as Interferon [INF]-gamma, Interleukin [IL]-12 and tumor necrosis factor [TNF]-alfa. Therefore, like for other urological cancers, the clinical response to intravesical BCG administration seems to be linked to the efficiency of the immune system.

Senesce has been reported to negatively affect the immune system and, therefore, to have a potential negative effect on BCG efficiency. Indeed, current EAU Guidelines point out that BCG efficiency is reduced in patients ≥ 70 years old, thus making treatment of such patients quite challenging. In clinical practice, this often leads to elderly patients with high-risk NMIBC to receive no adjuvant treatment after TURBT or, in some cases, to undergo immediate cystectomy, a major surgery with a significant impact on patients’ quality of life as well as a significant risk of complications.

The present study aimed to determine whether elderly patients (≥ 70 years) with high-grade T1 BC benefit from adjuvant intravesical instillation of BCG.

MATERIALS AND METHODS

We retrospectively analyzed our prospectively maintained NMIBC database to identify patients with high-grade T1 BC (according to 2004 WHO grading) aging ≥ 70 years. After TURBT, all patients were offered adjuvant treatment by intravesical instillations of BCG, initially Pasteur strain, 75 mg in 50 mL saline, and later on RIVM strain, 81 mg in 50 mL saline. Patients who accepted received the classical six-week induction cycle and underwent bladder biopsies/TUR 5-8 weeks after having completed it. Those who responded to the induction cycle underwent maintenance according to EAU Guidelines. Those who refused adjuvant BCG underwent follow-up.

Follow-up consisted of urine cytology and cystoscopy every 3 months for the first two years, every 6 months for the third year, and then yearly. Chest and abdominal computed tomography was performed at initial diagnosis and then every year to rule out upper tract or metastatic disease. Tumor recurrence was defined as pathological evidence of disease at bladder biopsy or TURBT, whereas tumor progression was defined as pathological shift to muscle invasive disease at bladder biopsy or TURBT or imaging techniques demonstrating recurrent bladder cancer and distant metastasis likely related to it.

Two senior pathologists unaware of clinical data reviewed all specimens including agreement with the latest WHO Classification of Tumors of the Urinary System and Male Genital Organs and the 2010 TNM staging system. The study was approved by the Internal Review Board.

STATISTICAL ANALYSIS

Continuous data are reported as means ± standard deviations (SD) or median values as appropriate; those with normal distribution according to the Skewness and Kurtosis test were compared by Student’s t-test whereas those with a non-parametric distribution were compared by the Mann-Whitney U-test. Differences in rates were compared by the chi-square test or the Fisher’s exact test. Univariate analysis of disease free survival (RFS), progression free survival (PFS) and cancer specific survival (CSS) was carried out using the Kaplan-Meier method, with differences among groups being tested for significance using the Log-rank test. Univariate and multivariate Cox’s proportional hazard regression analysis was carried out to test the impact of clinical variables on RFS, PFS and CSS. Significance was set at p < 0.05. Statistical analysis was carried out using the MedCalc 16.8 Software (MedCalc, Ostend, Belgium) and STATA SE 14.

RESULTS

Between January 2005 and June 2018, a total of 199 patients aging ≥ 70 were diagnosed with high-grade T1 BC. Their median age at diagnosis was 79 years (range 70-96). One hundred-eight patients underwent restaging trans-urethral resection (Re-TUR) whereas 91 refused it; residual/recurrent BC was found in 57 (52.7%), muscle-invasive (T2) BC in 6 (5.5%), and no residual tumor in 45 (41.8%). The 6 patients with T2 disease and the 4 with high-grade T1 and concomitant Carcinoma in situ (CIS) at Re-TUR underwent cystectomy. Of the remaining 189 patients, 71 underwent BCG induction therapy whereas 118 patients refused it. Six patients did not complete BCG induction cycle due to recurrent cystitis or poor compliance, thus were excluded. Study population therefore consisted of 183 patients, 65 treated and 118 not treated with BCG; their clinical characteristics are reported in Table I. Their median follow-up was 45 (1-177 months).

Kaplan-Meier plots pointed out that treated patients had significantly better RFS and PFS (Fig. 1). Of the 40 patients who progressed, 22 underwent cystectomy; eventually, 18 patients died because of their BC. The 40-month CSS was 86.2% in treated and 79.7% in untreated patients (p = 0.274) and Kaplan-Meier plots confirmed that such difference in CSS was not statistically significant (Fig. 1).
Treating high-grade T1 bladder cancer in the elderly. Is intravesical instillation of BCG worth?

At univariate Cox’s proportional hazard regression analysis, Re-TUR and BCG treatment were the only significant predictors of RFS and PFS, whereas age, sex, tumor presentation, size and number, CIS, presence of muscle in the first sampling had no predictive value (Tab. II). At multivariate analysis, BCG treatment remained a statistically significant independent predictor of both RFS and PFS whereas Re-TUR significantly predicted PFS but not RFS (Tab. III).

No serious BCG-related adverse reaction (AR) was observed. Two (3.1%) patients suffered mild ARs consisting in flu-like symptoms (fever, malaise) lasting < 24 hours, mild bladder pain and moderate low urinary tract symptoms of the storage phase (nocturia, frequency, urgency). All reactions resolved with symptomatic treatment, namely paracetamol 1 gr twice-a-day, within two days.

DISCUSSION

The present study pointed out that elderly (≥ 70 years old) patients with high-grade T1 BC benefit from adjuvant BCG treatment in terms of RFS and PFS.

The question of BCG efficacy in the elderly has been raised by a few studies theorizing that senescence may deteriorate the innate and adaptive immune systems thus leading to a reduced response to BCG treatment. Evidence is to date controversial. In a large study on 805 patients, Herr et al. reported no difference in initial response to BCG; 5-year cancer free rate was 25% in patients ≥ 70 years compared with 37% in patients < 70 years but there was no difference in PFS and CSS. This study however included both Ta and T1 high-grade tumors and excluded patients with early failure. Margel et al. compared patients < 75y with those ≥ 75y and found no difference in RFS but a statistically significant (p < 0.001) difference in PFS. Cox multivariate proportional hazard regression analysis demonstrated that age was the most significant independent predictor of progression (HR 2.1) followed by BCG maintenance (HR 0.8). However, this study included both low-grade and high-grade tumors, Ta, T1 and CIS, and no survival curves adjusted for prognostic factors were provided.

Finally, Oddens et al. reported that, at mean follow-up of 9.2y, age did not affect RFS but patients > 70y had a worst PFS and CSS than those < 70y. However, also
this study has the limitations of having included both low-grade and high-grade tumors, stage Ta and T1. Findings from the above-mentioned studies, particularly the latter, have led to questioning the opportunity of offering BCG to patients with high-grade NMIBC. The present study did not aim to determine whether age impacts on BCG efficacy but rather how should we treat elderly patients with high-grade T1 BC. Findings were clear. BCG treatment provided significant benefit in terms of RFS and PFS at the price of a low rate of mild ARs. BCG treatment provided a non-significant benefit in CSS; this could be due both to the small number of events and careful follow-up having avoided delays in cystectomy in case of progression. Like for other common urological conditions, case volume, tailor- ing treatment to patients clinical conditions and wise clinical judgment all play an essential role. Indeed, a previous study testing BCG treatment in elderly patients reported better CSS in patients who received BCG than in those who did not; unfortunately, also this study suffered the limitations of having included both low-grade and high-grade tumors, stage Ta and T1. Another relevant yet controversial question is BCG toxicity in the elderly. Heiner et al. pointed out that BCG complications were significantly (p = 0.001) more common in elderly patients, thus recommending to treat such patients by BCG induction only or even by “other” intravesical agents. Racioppi et al. found that elderly patients had more early complications but the rate of severe complications did not vary with age. However, they recommended administering the BCG induction cycle biweekly in the elderly patients to reduce the risk of complications. Finally, a recent large study on patients randomized to receive 3 years BCG maintenance pointed out no impact of age on treatment side effects or discontinuation.

In the present study, treatment discontinuation during the induction cycle occurred in 8.5% (6/71) of our elderly patients. In view of previous studies, this seemed to be appropriate. Another was

### Table II. Cox univariate proportional hazards regression analysis of possible confounding variables.

<table>
<thead>
<tr>
<th></th>
<th>Recurrence free survival</th>
<th>Progression free survival</th>
<th>Cancer specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.60 (0.27-1.30) 0.196</td>
<td>0.89 (0.34-2.27) 0.810</td>
<td>1.24 (0.47-3.24) 0.652</td>
</tr>
<tr>
<td>Primary</td>
<td>0.81 (0.47-1.38) 0.435</td>
<td>1.36 (0.60-3.09) 0.455</td>
<td>1.64 (0.81-3.30) 0.163</td>
</tr>
<tr>
<td>Single</td>
<td>0.89 (0.56-1.43) 0.652</td>
<td>0.83 (0.43-1.56) 0.560</td>
<td>4.03 (0.85-19.1) 0.078</td>
</tr>
<tr>
<td>Tumor size (&gt; 3 cm)</td>
<td>1.16 (0.59-2.30) 0.656</td>
<td>1.42 (0.49-4.14) 0.514</td>
<td>0.89 (0.12-6.54) 0.906</td>
</tr>
<tr>
<td>CIS</td>
<td>0.27 (0.03-1.98) 0.200</td>
<td>0.64 (0.08-4.70) 0.664</td>
<td>1.00 (0.43-2.31) 0.990</td>
</tr>
<tr>
<td>Muscle*</td>
<td>1.06 (0.59-1.90) 0.837</td>
<td>1.06 (0.49-2.30) 0.881</td>
<td>0.28 (0.12-0.63) 0.002</td>
</tr>
<tr>
<td>Re-TUR</td>
<td>0.59 (0.37-0.95) 0.030</td>
<td>0.38 (0.19-0.73) 0.004</td>
<td>0.28 (0.12-0.63) 0.002</td>
</tr>
<tr>
<td>BCG</td>
<td>0.44 (0.26-0.76) 0.003</td>
<td>0.29 (0.13-0.67) 0.004</td>
<td>0.58 (0.27-1.25) 0.165</td>
</tr>
</tbody>
</table>

*CIS: carcinoma in situ; BCG: Bacillus Calmette-Guérin; Re-TUR: Restaging Transurethral Resection; Presence of muscle in the sample on first TURBT.

A strong point of our study was having focused on a very homogeneous cohort of patients with high-grade T1 BC and having taken into account available prognostic factors such as sex, primary tumor, concomitant CIS, tumour size and number, as well as Re-TUR. One potential study limitation was the use of an arbitrary cut-off of 70 years but, in view of previous studies, this seemed to be appropriate. Another was

### Table III. Cox multivariate proportional hazards regression models of possible confounding variables.

<table>
<thead>
<tr>
<th></th>
<th>Recurrence free survival</th>
<th>Progression free survival</th>
<th>Cancer specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
</tr>
<tr>
<td>Re-TUR</td>
<td>0.68 (0.42-1.08) 0.108</td>
<td>0.43 (0.22-0.85) 0.016</td>
<td>0.38 (0.15-0.95) 0.124</td>
</tr>
<tr>
<td>BCG</td>
<td>0.48 (0.27-0.83) 0.009</td>
<td>0.34 (0.14-0.77) 0.011</td>
<td>0.81 (0.3-1.12) 0.174</td>
</tr>
</tbody>
</table>

BCG treatment is a significant independent predictor of RFS and PFS. Whereas Re-TUR predicted PFS but not RFS. BCG: Bacillus Calmette-Guérin; Re-TUR: Restaging Transurethral Resection.
not having assessed the impact of other potential predictors of disease outcome, including smoking habits, and molecular markers having proved to be reliable in this setting, but they are not routinely assessed and a dedicated analysis seemed to be beyond the scope of this clinical study.

In conclusion, elderly (≥ 70y) patients with high-grade T1 BC seem to benefit from adjuvant BCG treatment. Given the low rate of mild ARs, age per se should not be considered an absolute contraindication to such treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References


SHORT COMMUNICATION

Radical prostate cancer treatment in the elderly: role of cryotherapy

G. Silecchia1, O. Selvaggio1, G. Stallone2, F. Lugnani3, A. Hoznek4, G. Carrieri1.

1 Urology and Renal Transplantation Unit; Department of Medical and Surgical Sciences, University of Foggia, Italy; 2 Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 3 Department of Urology, Kirurski Sanatorij Ljubljana, Slovenia; 4 Department of Urology, Henri Mondor Hospital, Créteil, France

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men. In the era of PSA screening, predictive models 1-5, novel imaging techniques 6 and biomarkers 7-10 the PCa detection rate has dramatically increased. Although many elderly men who are diagnosed with PCa will die from other causes, 70% of PCa-related deaths occur in men aged > 75 years 11,12 and PCa remains the third cause of death in male 13. Moreover, many men who do not die from Pca will suffer significant morbidity related to this disease. Treatment of PCa in the elderly therefore represent a major clinical issue. Though improvement of detection methods could lead to the risk of overtreating low-risk disease, evidence suggest that elderly men tend to be undertreated 14.

Background & Aims. Data regarding efficacy and safety of radical cryotherapy for localized prostate cancer in elderly men are lacking. This study aimed to determine oncological and functional outcomes of radical cryotherapy in this setting.

METHODS. From our dedicated Internal Review Board approved prospectively maintained database we selected elderly (> 75 years) patients with localized prostate cancer as assessed by a negative staging choline-PET. After cryotherapy, patients were seen at 1 month, every 3 months for the first two years, then every six months, for clinical examination, serum PSA, questionnaires for lower urinary tract symptoms (IPSS) and erectile function (IIEF-5), and assessment of pad usage for urinary continence. Biochemical recurrence was defined as a rising PSA above the Nadir of more than 2 ng/mL. Complications were scored using the Clavien-Dindo scale.

RESULTS. From March 2012 to June 2018, 45 patients met the inclusion criteria. Mean postoperative hospital stay was for 1.06 days. At median follow-up (41 months), biochemical failure occurred in 8.8% of patients, with Kaplan-Meier plots showing an estimated 85% biochemical-free survival at 5y. Three (6.6%) patients reported urge urinary incontinence needing at least 2 pad/day; they were treated by antimuscarinic agents with complete symptoms resolution in 2 and relevant benefit in one. No patient suffered stress urinary incontinence.

Conclusions. This is the first study testing radical cryoaablation in the setting of elderly patient. It showed excellent 5y biochemical recurrence-free survival not only in intermediate-risk but also in high-risk patients at the price of a reasonable/low rate of minor complications.

Key words: Elderly, Cryotherapy, Prostate cancer, Prostate biopsy
Indeed, the lower cancer-specific survival (CSS) observed in elderly men may be at least partly explained by underuse of radical, therefore potentially curative, local treatments. Moreover, elderly patients are more likely than younger patients to be diagnosed with aggressive cancers.

The International Society of Geriatric Oncology recommends that patients should be managed on the basis of their health status rather than on chronological age alone. Similarly, the European Association of Urology (EAU) guidelines for the management of prostate cancer in older men recommend that the treatment decision process should take into account the risk of dying from prostate cancer, potential adverse effects of treatment, and patient preference. Baseline health status and life expectancy should also be carefully evaluated to determine whether or not the patient is fit for treatment. Having said this, chronological age is often used as a cut-off in the screening, diagnosis and management of prostate cancer; with the 10 years life expectancy criterion remaining a standpoint in indicating radical treatment. Indeed, radical prostatectomy (RP) is usually not offered in men with a < 10 years life-expectancy due to the perceived lack of oncological benefit and the risk of debilitating side-effects.

External beam radiotherapy seems to provide similar cancer control regardless of age but a dose of > 72 Gy should be given by intensity-modulated or image-guided RT. After such dose gastrointestinal (GI) and urinary side-effects are common; approximately 50% of patients reported acute urinary side effects of Grade I, 20% Grade 2, and 2% of Grade 3. Moreover, approximately 30% of patients reported acute Grade I GI toxicity, 10% Grade 2, and less than 1% Grade 3. In other words, phenomena such as dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis are common. Also fatigue is common.

Cryotherapy is emerging as an effective minimally invasive treatment option for localized PCa treatment, though current EAU guidelines recommend it within the setting of clinical trials. The role of cryotherapy in the setting of elderly patients, however, has not been explored. Therefore, the present study aimed to determine oncological and functional outcomes of elderly men with localised Pca treated by radical cryotherapy.

PATIENTS AND METHODS

From our dedicated Internal Review Board approved prospectively maintained database of Prostate Cryotherapy we selected elderly (> 75y) patients who had undergone prostate biopsy at our Institution and were diagnosed with localized PCa as assessed by a negative staging PET-choline. Radical prostate cryotherapy was always carried out under spinal anesthesia. Depending on prostate volume, six to eight 2.4 mm cryoprobes were inserted into the prostate through the perineum under ultrasound (US) guidance. Radical ablation was obtained using an argon/helium gas-based system (Endocare, HeathTonics Inc., Austin, TX, USA); specifically, pressurized argon (300 bar of pressure and -180°C) exploited freezing, whereas both helium and room temperature were used to obtain thawing. Temperature was monitored inside and outside the prostate by sensors positioned in the apex, external sphincter, and neurovascular bundle on both sides. Injecting saline solution mixed with a broad-spectrum antibiotic in the Denonvilliers’ fascia (Onik maneuver) was used to separate the prostate from the rectum. Urethral temperature was kept at 38°C by a continuous flow system pumping saline solution at 41°C. Cryoablation usually involved two cycles of freezing/thawing but 7 (15.5%) patients with large prostate volume required a third cycle. All procedures were carried out by one of us (OS). At the end of the procedure, a Foley urethral catheter was left in place. Patients were scheduled for discharge on first postoperative day with the indwelling Foley catheter to be kept in place for ten days and prescribed painkillers as needed.

Patients were seen at 1 month postoperatively, every 3 months for the first two years, then every six months. Follow-up consisted in clinical examination, serum PSA, validated questionnaires for lower urinary tract symptoms (IPSS) and erectile function (IIEF-5), and assessment of pad usage for urinary continence. Biochemical recurrence was assessed using Phoenix criteria and defined as a rising PSA above the Nadir of more than 2 ng/mL.

RESULTS

From March 2012 to June 2018, a total of 45 patients met the inclusion criteria. Their descriptive characteristics are summarized in Table I. Median age was 79 years, median preoperative PSA was 5.8 ng/dL, median total percentage of cancer (TPC%) was 16.5 and median prostate volume was 44 cc. Clinical stage was cT1c in 23 patients, cT2b in 1, cT2c in 20, and cT3a in 1. Finally, Gleason Group (GG) was 1 in 17.8% of patients, 2 in 24.4%, 3 in 17.8%, 4 in 33.3%, and 5 in 6.7%.

Mean postoperative hospital stay was for 1.06 days as 3 patients were discharged on second postoperative...
Radical prostate cancer treatment in the elderly: role of cryotherapy

At median follow-up of 41 months, biochemical failure occurred in 4 (8.8%) patients, with Kaplan-Meier plots showing an estimated 85% biochemical-free survival at 5y (Fig. 1). Patients with biochemical failure were offered multiparametric MRI and prostate re-biopsy. One refused them as well as further treatment and follow-up; the other 3 underwent prostate biopsy and were diagnosed with prostate cancer. Two underwent second radical cryotherapy while the third elected to undergo androgen deprivation treatment.

Changes in median IPSS and IIEF-5 score are reported in (Fig. 2). Pre-operatively, 9 patients reported mild Erectile Dysfunction (ED) and 2 no ED; at 12-month follow-up, only 1 reported mild ED and none no ED. Three (6.6%) patients reported urge urinary incontinence needing at least 2 pad/day; they were treated by antimuscarinic agents with complete symptoms resolution in 2 and relevant benefit in one. No patient suffered stress urinary incontinence.

**DISCUSSION**

Radical treatment of localized prostate cancer in men over 75 years is a controversial issue. Several factors such as treatment efficacy and safety, life expectancy, and the postulated marginal cancer-specific survival benefit need to be taken in due account. The present study pointed out that radical cryotherapy provided, in elderly patients with localized PCa, a 5y biochemical recurrence-free survival of 85%. This result is particularly encouraging considering that 40% of...
patients had a high-risk disease, given their GG 4 and 5. Indeed, all 4 biochemical failures occurred in patients with high-risk disease, specifically 2 in patients with GG4 and 2 with GG5. These data suggest that elderly men with localized high-risk prostate cancer may benefit from this local treatment. Our 77.8% 5y biochemical recurrence-free survival in high-risk patients compares well with the biochemical recurrence-free survival reported after radical prostatectomy for high-risk prostate cancer, which ranges from 58.4\textsuperscript{27} to 85%\textsuperscript{28}. This is of great clinical relevance in view of the fact that, as mentioned above, radical prostatectomy is usually not offered to elderly patients due to the perceived lack of oncological benefit and the risk of procedure-related complications\textsuperscript{29}, though their occurrence, like for most surgical procedures, is much linked to case volume\textsuperscript{30}. Indeed, elderly patients with high-grade localized PCAs are usually offered radiotherapy or androgen deprivation treatment (ADT) or both. Radiotherapy may be an attractive treatment option for patients who cannot tolerate surgery. The reported 5y biochemical recurrence-free survival for radiotherapy in high-risk PCAs, however, is 52.7%\textsuperscript{31}, quite lower than the one we obtained. Apart from efficacy in high-risk PCAs, counseling regarding radiotherapy should take into account its common GU and GI side-effects as well as the unpleasant sense of fatigue. Though the incidence of radiotherapy associated adverse effects do not seem to increase with age\textsuperscript{12}, patients with peripheral vascular disorders seem to be at higher risk of complications following this treatment.

The scenario is not that different for ADT that may involve metabolic disturbances and even severe cardiovascular events\textsuperscript{32-34}. These harmful effects of ADT are cumulative, with the most significant survival disadvantage seen in those with comorbidity-adjusted life expectancy of >10 years. Nevertheless, a significant proportion of older men with localized prostate cancer are treated with ADT, which denies them the opportunity to receive radical treatment while exposing them to the devastating side-effects of such treatment. Of course, the combination of radiotherapy and ADT, which is recommended in high-risk disease, may expose to all such adverse events. Not to mention treatment duration, which is obviously much longer for both radiotherapy and ADT when compared with cryotherapy. Taken together, these considerations would strongly support a role for cryotherapy in elderly patients with high-risk localized PCAs.

More complex is the issue of radical treatment in elderly males with low or intermediate risk localized PCAs. While active surveillance (AS) seems to be a reasonable option in patients with GG1, even when not all standard criteria\textsuperscript{35,36} for AS are meet, counseling becomes a bit more difficult in patients with intermediate risk disease. On one hand, elderly men, especially those with chronic comorbid conditions, are likely to die from other causes rather than their PCAs. On the other hand, however, increase life expectancy and the risk of biopsy having downgraded the tumor question AS. In this scenario, the possibility of offering a minimally-invasive approach having a 100% 5y biochemical recurrence free rate, as we had no failure in patients at intermediate risk, is definitely appealing. Not to mention that most patients are happy to receive a minimally-invasive yet potentially curative treatment for their cancer rather than live with it untreated. Finally, side-effects were not common and, in any case, minor. Of course, clinical factors predicting treatment outcome\textsuperscript{37} and wise clinical judgement remain essential like in other common urological procedures\textsuperscript{38-40}.

This study is not without limitations. First, it is a single centre study with a relatively small number of patients; however, this allowed stringent inclusion criteria. Second, it is retrospective but data were prospectively collected.

In conclusion, this is to our knowledge the first study testing radical cryoablation in the setting of elderly patient. Cryotherapy provided an excellent 5y biochemical recurrence-free survival not only in intermediate-risk but also in high-risk patients at the price of a reasonable if not low rate of minor complications.

**ConFLICT OF INTEREST**

The authors declare no conflict of interest.

**References**

Radical prostate cancer treatment in the elderly: role of cryotherapy


Robot-assisted pelvic lymphadenectomy for prostate cancer. Potentially advantageous in the elderly?

M. Di Nauta¹, L. Cormio¹, R. Villani², V. Mancini¹, E. Barret³, G. Carrieri¹

¹ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Department of Clinical and Experimental Medicine, University of Foggia, Italy; ³ Department of Urology, Institut Montsouris, Paris, France

INTRODUCTION

The most effective method for detecting lymph node metastases in prostate cancer (PCa) remains pelvic lymph node dissection (PLND). This procedure allows having precise staging and consequent prognostication, thus guiding the postsurgical decision-making process ¹ ². Recent years have seen a decline in PLND during radical prostatectomy (RP). While this has been mainly attributed to PCa stage migration occurring in the prostate-specific antigen (PSA) screening era, question remains whether this has also been the result of the introduction of training programs in novel minimally-invasive procedures such as laparoscopic and robotic-assisted radical prostatectomy ³. Indeed, although the feasibility of PLND during robot-assisted radical prostatectomy (RARP) has been well demonstrated ⁴, patients undergoing open retropubic radical prostatectomy (RRP) were more likely to have concomitant PLND than patients undergoing minimally invasive RP ⁵-⁷. Moreover, as much as 20% of surgeons performing both open and robotic approaches, declare that the indication for and the extent of their PLND depends on the approach they elect to use ⁸.

Background and Aims. Pelvic lymphadenectomy is the most effective method for the detection of lymph node metastases due to prostate cancer. Question remains whether robot-assisted pelvic lymphadenectomy provides the same number of nodes than open lymphadenectomy. We compared outcomes and number of nodes retrieved by the two procedures.

Methods. Data of patients who had undergone pelvic lymphadenectomy during robot-assisted radical prostatectomy (Group A) between January 2016 and June 2018 were compared to those of a matched population having undergone pelvic lymphadenectomy during open retropubic prostatectomy (Group B).

Results. The median number of removed lymph nodes was 11 (range 8-15) in Group A and 14 (range 12-16) in Group B (p = 0.05) but the rate of N+ patients was 11.4% in Group A and 14.7% in group B (p = 0.3). The median number of metastatic lymph nodes was 1 (range 1-1) in Group A and 2.2 (range 1-9) in Group B. There was no vascular complication but the rate of lymphocele requiring percutaneous drainage was 9% in Group B as opposed to none in Group A (p = 0.12) and mean age of patients suffering this complication was 70y.

Conclusions. Robot-assisted pelvic lymphadenectomy provided a lower number of nodes than the open approach but this did not significantly change the number of patients diagnosed as N+. Though more time-consuming, the robotic approach avoided pelvic lymphoceles which were seen in almost 10% of patients having undergone the open approach. The risk of such complication appeared to be related to age.

Key words: Elderly, Prostate cancer, Radical Prostatectomy, lymphadenectomy, robotic surgery, open surgery
Potential reasons for PLND being less common during RARP include increased operative room time and costs and the risk of vascular complications, particularly in patients aging > 65y as they are more likely to have vascular comorbidities. Moreover, skipping PLND may be linked to the need of shortening surgical time in patients with reduced respiratory capacity; again, this is more common in patients aging > 65y. The same reasons might also lead to a less aggressive dissection, thus resulting in a lower number of removed nodes. Surgical volume and learning curve may also play a relevant role in determining the number of retrieved nodes.

To determine whether RARP allows to retrieve a number of nodes similar to RRP, in the present study we compared the yields of nodes of the two procedures.

**PATIENTS AND METHODS**

Data of patients scheduled for RP at our institution from January 2016 to June 2018 were entered into our prospectively maintained, Internal Review Board approved database. To avoid potential inclusion biases, we carried out a retrospective analysis of only those patients who had undergone prostate biopsy (PBx) at our institution. Accordingly, all included patients had undergone PSA measurement before DRE and transrectal ultrasound (TRUS) as well as to uroflowmetry (UFM) unless they had an indwelling urethral catheter \(^{9-12}\). PBx was carried out under local non-infiltrative anesthesia \(^{13}\), TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme \(^{15}\). A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate \(^{16}\), and PCa.

Patients diagnosed with PCa and considered eligible for radical prostatectomy received PLND if they had a clinically-significant PCa defined as those with a Gleason Grade Group (GGG) > 1 according to the International Society of Urological Pathology (ISUP) consensus \(^{17}\). The dissection aimed to remove the obturator, internal iliac and external iliac nodes, from the cross of the ureter over the common iliac artery to the inguinal ring. Our dedicated pathologist (FS) analysed all specimens. Data of patients having undergone robot-assisted PLND were compared with those having undergone PLND during RRP over the same period.

**STATISTICAL ANALYSIS**

Continuous variables are reported as medians and interquartile range and analyzed by the Mann Whitney U test. Categorical variables are reported as frequencies and analyzed by the Chi square Test. Statistical Analyses were performed using STATA 14 (StataCorp LP, College Station, TX, USA). Significance was set at \(\alpha = 0.05\).

**RESULTS**

A total of 35 patients underwent robot-assisted PLND (Group A); they were compared to a matched population of 34 patients who underwent PLND during RRP over the same time period (Group B). Baseline characteristics of the two populations are shown in Table I. There was no difference between the two Groups in Age, preoperative PSA, Suspicious DRE rates and Biopsy Gleason Grade group. Although we did not record surgical time for PLND, the robotic approach certainly took longer than the open one. However, no vascular complication occurred with both approaches, but 3 (9%) patients in Group B had pelvic lymphoceles requiring percutaneous drainage.

Final pathology (Tab. II) showed that the number of retrieved nodes was higher in the open approach than in the robotic one (11 vs 14, respectively; \(p = 0.05\)) but there was no difference in the rate of patients classified as node-positive (pN+) which was 14.7% for the open approach and 11.4% for the robotic one \((p = 0.7)\). The median number of metastatic lymph nodes was 2.2 (range 1-9) for the open approach and 1 (range 1-1) for the robotic one.

**DISCUSSION**

The main goal of PLND in PCa is to optimize locoregional staging; this allows to identify patients at risk of progression who may therefore benefit from adjuvant treatment. Evidence suggests that the more is the number of removed nodes, the greater is the chance of detecting lymph node metastasis but the ideal number of lymph nodes that need to be removed for adequate PCa staging remains unclear. Autopsy series suggests that 20 nodes must be removed for accurate locoregional staging \(^{18}\).

In spite of the availability of novel biomarkers \(^{19-21}\), the risk of a patient with PCa having lymph node metastasis remains linked to standard clinic-pathological factors. Indeed, the Briganti nomogram \(^{22}\) remains the most effective method to predict the risk of lymph node metastasis and therefore to perform PLND during RP. A simplified approach involves offering PLND to patients with clinically-significant PCa. However, like for other common urological conditions, the decision
Robot-assisted pelvic lymphadenectomy for prostate cancer. Potentially advantageous in the elderly?

...to perform PLND often relies on patients local conditions and wise clinical judgment. This turns on the above-mentioned data of 20% of surgeons modulating the indication for and the extent of their PLND on the approach they elect to use.

Question remains on the ability of the robotic approach to provide the same number of nodes yielded by open one. Indeed, Zorn et al. noted that overall lymph node yield was significantly lower (12.5 vs 15 nodes) during RARP than in an historical cohort of open procedures. Similar findings were reported in other studies and such differences remained significant after adjustment for disease characteristics. Conversely, Polcari et al. found no difference in terms of lymphnode yield and probability of finding positive lymphnodes between robot-assisted and open RP. Similarly, Truesdale et al. demonstrated that, when patients were stratified for preoperative D’Amico risk criteria, the number of removed lymph nodes was statistically comparable between RARP and RRP, particularly when the analysis was restricted to patients having received an extended PLND. Katz et al. published similar results.

In an attempt to summarise available evidence, Piousard et al. performed a systematic review of the literature and concluded that PLND during RARP can be performed effectively and safely. The overall number of nodes removed, the likelihood of node positivity, and the types and rates of complications of PLND were similar to those of pure laparoscopic and open retropubic procedures.

Our study pointed out that open PLND allowed to retrieve a greater number of nodes (14 vs 11, respectively; p = 0.05) than the robot-assisted one, but this did not turn into a significant difference in the rate of patients...

Table I. Patients characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A = robotic (n = 35)</th>
<th>Group B = open (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>64 (60-71)</td>
<td>67 (59-71)</td>
<td>0.5</td>
</tr>
<tr>
<td>PSA (ng/mL)*</td>
<td>7.0 (5.6-9.6)</td>
<td>6.5 (4.5-11.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Suspicious DRE, n (%)</td>
<td>21 (60%)</td>
<td>18 (52.9%)</td>
<td>0.5</td>
</tr>
<tr>
<td>GGG** Biopsy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (14.3%)</td>
<td>4 (11.8%)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>11 (31.4%)</td>
<td>11 (32.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (20.0%)</td>
<td>6 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 (25.7%)</td>
<td>9 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (8.6%)</td>
<td>4 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (mL)*</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>40.0 (33.0-53.0)</td>
<td>41.3 (31.0-62.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as medians (Interquartile Range). ** GGG: Gleason grade group.

Table II. Final pathology results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A = robotic (n = 35)</th>
<th>Group B = open (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2a</td>
<td>1 (2.9%)</td>
<td>5 (14.7%)</td>
<td>0.3</td>
</tr>
<tr>
<td>pT2b</td>
<td>5 (14.3%)</td>
<td>4 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>pT2c</td>
<td>14 (40.0%)</td>
<td>15 (44.1%)</td>
<td></td>
</tr>
<tr>
<td>pT3a</td>
<td>7 (20.0%)</td>
<td>7 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>pT3b</td>
<td>8 (22.9%)</td>
<td>3 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>GGG**, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (14.3%)</td>
<td>5 (14.7%)</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>15 (42.9%)</td>
<td>13 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (17.1%)</td>
<td>6 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (14.3%)</td>
<td>8 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4 (11.4%)</td>
<td>2 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Total n. of nodes*</td>
<td>11.00 (8.0, 15.0)</td>
<td>14.00 (12.0, 16.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>pN1 patients, n (%)</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>4 (11.4%)</td>
<td>5 (14.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as medians (Interquartile Range). ** GGG: Gleason grade group.
classified as node-positive (14.7% for the open approach and 11.4% for the robotic one). It is worth mentioning that we analysed just the first 35 consecutive cases of our robotic experience, and case load is known to play a key role in almost all surgical procedures. Also, we did not experience more complications with the robotic approach in spite of potential specific complications of this procedure are well known. Conversely, the robotic approach prevented lymphoceles requiring percutaneous drainage, which were seen in 9% of patients having undergone the open approach. This may be a potential advantage of the robotic approach in patients aged > 65y, since the mean age of patients who suffered lymphoceles requiring percutaneous drainage was 70y. Our study is not without limitations. First, the number of patients is small but we aimed to evaluate the outcome of the initial phase of our robotic experience, assuming we can only do better by time. Second, surgeon's and pathologist's diligence may impact on the number of nodes retrieved; however, this was a single-surgeon experience (GC) with a single pathologist reviewing all specimens. In conclusion, robot-assisted PLND proved to be safe and effective even during the learning curve. Though providing a lower number of nodes, it did not significantly affect correct N staging. The robotic approach seemed to be safer than the open one since it prevented lymphocele occurrence, which was found to be a common complication of the elderly probably due to impaired vascular and lymphatic status. However, it should be taken into account that the robotic approach is time consuming and this may be relevant in patients with significant preoperative comorbidity, like the elderly, whereby surgical time may be an issue.

Acknowledgements
We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

Conflict of Interest
The authors declare no conflict of interest.

References
SHORT COMMUNICATION

Multiparametric magnetic resonance imaging/transrectal ultrasound fusion-guided prostate biopsy: a comparison with systematic transrectal ultrasound-guided prostate biopsy

G. Silecchia1, U. Falagario1, F. Sanguedolce2, L. Macarini3, R. Autorino4, L. Cormio1

1 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 2 Section of Pathology, Department of Clinical and Experimental Medicine, University of Foggia, Italy; 3 Department of Radiology, University of Foggia, Italy; 4 Division of Urology, Department of Surgery, VCU Health, Richmond, VA, USA.

Background & Aims. Prostate biopsy is the standard method for diagnosing prostate cancer. Herein we compared the cancer detection rate of extended systematic Transrectal Prostate Biopsy with that of multiparametric Magnetic Resonance Imaging/Transrectal ultrasound fusion-guided Prostate biopsy.

Methods. Outcomes of 99 fusion prostate biopsy (Group A) were compared with those of a matched population of patients having undergone systematic transrectal prostate biopsy (Group B) in the same period.

Results. The overall cancer detection rate was 60.6% in Group A and 29.2% in Group B (p = < 0.001) whereas the rate of clinically-significant prostate cancer was 26.2% in Group A and 13.1% in Group B (p = 0.02). At first prostate biopsy the above-mentioned rates were 76% in Group A and 31.9% in Group B (p < 0.001), whereas in repeated biopsy the rates were 34.7% in Group A and 18.6% in Group B (p = 0.08). Cancer detection rates correlated well with the Prostate Imaging-Reporting and Data System; in the setting of first biopsy, it was 84.6, 67.8, 100% for score 3, 4 and 5, respectively, whereas in the setting of repeat biopsy it was 28.5, 55.5 and 80% for score 3, 4 and 5, respectively. Complications rate was similar in both groups but all occurred in patients > 75y.

Conclusions. Multiparametric Magnetic Resonance Imaging/transrectal ultrasound fusion-guided biopsy provided better prostate cancer detection rates than standard Prostate Biopsy in the setting of both first and repeated Prostate Biopsy, showing good correlation between Prostate Imaging-Reporting and Data System scores and cancer detection rates but complications were more common in elderly patients.

Keywords: Prostate Cancer, Magnetic Resonance Imaging, fusion biopsy, systematic biopsy, detection rate

INTRODUCTION

Prostate cancer (PCa) represents the tumor with the highest incidence in Italy and its incidence significantly increase with age. Physicians however tend to be reluctant to recommend serum prostate-specific antigen (PSA) testing in men > 75 years as well as to advise prostate biopsy for increased PSA levels; this is even more true for those with PSA in the grey zone (4-10 ng/ml) who suffer from lower urinary tract symptoms (LUTS). Such reluctance is likely associated to the perception of most PCas in the elderly being clinically insignificant.

Multiparametric magnetic resonance imaging (mpMRI) of the prostate is increasingly been used in the assessment of patients at risk of being diagnosed with PCa...
given its postulated ability to identify such neoplasm, particularly high-grade disease. The diagnosis of PCa however relies on prostate biopsy (PBx) but the diagnostic yield of Transrectal Ultrasound (TRUS) guided PBx remains low. In current clinical practice the cancer detection rate (CDR) of a first extended TRUS-guided systematic PBx prompted by an elevated PSA level and/or an abnormal digital rectal examination (DRE) is in the range of 40% 2, dropping to approximately 25% in the setting of screening programs, i.e. patients with serum PSA between 2.5 and 10 ng/mL 3. Efforts to improve the diagnostic yield of PBx have been oriented towards the construction of predictive models combining serum PSA and DRE findings with other readily available clinical information such as age, prostate volume (PVol), %freePSA etc., but also towards the development of novel tools including biomarkers 4 and imaging techniques. mpMRI findings seem to increase the accuracy of models predicting PBx outcome 5. Most important, the possibility of fusing mpMRI and TRUS images to guide PBx, the so-called fusion PBx, has been suggested to significantly increase significantly PBx CDR 6. The optimal clinical application of mpMRI, however, remains under investigation. According to current EAU guidelines 7, despite the use of the new PIRADS v2 scoring system, mpMRI has a low specificity, with high rates of false positives, especially among lesions scored 3/5 and 4/5. Moreover, the inter-reader reproducibility is moderate, limiting its broad use outside expert centres. Having said this, EAU guidelines recommend it before repeat biopsy (evidence level 1°; grade A). In the present study we evaluated our experience with mpMRI/TRUS fusion-guided PBx comparing its outcome with that of “standard” systematic TRUS guided PBx in the setting of both first and repeat PBx.

**PATIENTS AND METHODS**

Data of patients scheduled for TRUS-guided transrectal PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database. The present study is a retrospective comparison of the first 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) with a matched population of patients having undergone standard systematic TRUS-guided PBx (Group B) in the same period. 

MpmMRI was carried out using Intera Achieva by Philips with 1.5 tesla magnetic field strength, in T2WI, DWI axial at 3 b values and DCE-MRI (3Dt1W-THRIVE). PBx was carried out under local non-infiltrative anestheisia 8 9. TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme 10. In Group A, care was taken to identify the position of the index lesion(s) within our 18-core scheme and to take 2 cores from it using the Navigo™ Workstation (UC-CARE Medical System). Two senior uropathologists blind to procedural data evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate 11, and PCa.

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

**STATISTICAL ANALYSIS**

Continuous variables were compared by the Mann-Whitney U-test. Rates were tested by the Fisher’s exact test or the chi-square test, as appropriate. Statistical significance was set at p < 0.05. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

**RESULTS**

Table I reports the baseline characteristics of the 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) and those of a matched population of patients having undergone standard systematic TRUS-guided PBx (Group B). The percentage of patients aging > 75y was 20% in Group A and 17% in Group B. Procedural time was 37 ± 5.1 min in Group A and 11 ± 1.7 min in Group B (p < 0.001); there was no difference in complications rate (Group A 4% vs Group B 3%).

The overall CDR (Tab. II) was 60.6% in Group A and 29.2% in Group B (p < 0.001) whereas the rate of clinically-significant (csPCa), defined as cancers with Gleason sum ≥ 7 6, was 26.2% in Group A and 13.1% in Group B (p = 0.02). In the setting of first PBx, the overall CDR was 76% in Group A and 31.9% in Group B (p < 0.001) whereas the rate of csPCa was 34.7% in Group A and 18.6% in Group B (p = 0.08). In the setting of repeat PBx, the overall CDR was 47.1% in Group A and 26.9% in Group B (p = 0.032) whereas the rate of csPCa was 18.8% in Group A and 8.9% in Group B (p = 0.132). CDR correlated well with the Prostate Imaging-Reporting and Data System (PIRADS), being 50, 61.8 and 90% for PIRADS 3, 4 and 5 respectively in the overall population, specifically 84.6, 67.8 and 100% in the setting of first PBx, and 28.5, 55.5 and 80% in the setting of repeat PBx (Tab. III).
Complications were always minor. Macroscopic hematuria was observed in 2 (2%) cases and lasted 1-2 days. Rectal bleeding were also seen in 2 cases (2%). In one it required endoscopic clipping of a small artery, in the other Foley catheter balloon compression. There was one urinary tract infection which required specific antibiotic treatment. In 2 cases (2%) vasovagal symptoms as sweating, nausea, paleness, dizziness, and hypotension were observed. In all patients, these symptoms regressed when the patient was laid in the Trendelenburg position. Two patients (2%) suffered acute urinary retention treated by an indwelling Foley catheter for one week. All complications occurred in patients > 75y. Like for other procedures, the limited number of complications may be linked to our case volume.

**DISCUSSION**

The present study pointed out that mpMRI/TRUS fusion-guided PBx provided greater CDR than standard systematic PBx for overall PCa and csPCa in the setting of first and repeat PBx. Considering that this was our initial experience (first 99 cases) findings were quite satisfactory. Indeed, it has been reported that such results can be expected after having completed the learning curve of both radiologists and urologists with this procedure. Panebianco et al. reported a learning curve of approximately 50 cases whereas Canio et al. reported a learning curve of 270 cases. Furthermore, we recorded a very satisfactory correlation between PI-RADS scoring and CDR at PBx, somehow challenging the reported mpMRI low specificity and high rates of false positives between PI-RADS 3 and 4 lesions. Back to mpMRI indications, EAU guidelines recommend mpMRI before repeat biopsy (evidence level 1°; grade A) whereas its use in candidates for first PBx remains controversial. The initial and simplest method for mpMRI-targeted biopsy strategy is the cognitive approach. Three RCTs have compared a TRUS-guided PBx...
12-core PBx with a cognitive mpMRI-guided PBx in the setting of first PBx yielding conflicting results.16-18. The first two studies pointed out that CDR was higher in the mpMRI-guided group 17 18, whereas the most recent one showed that the two procedures provided comparable results 17.

The mpMRI/TRUS fusion software has been developed with the aim of providing a more precise sampling of the lesions identified by mpMRI. Initial non-randomized studies comparing mpMRI/TRUS fusion PBx with “standard” TRUS-guided PBx in the setting of first PBx pointed out that fusion PBx provided better CDR than “standard” PBx 19.20. The first RCT comparing mpMRI/TRUS fusion guided PBx with “standard” 12-core TRUS-guided PBx in the setting of first PBx (6) pointed out that “fusion” PBx provided a significantly greater overall CDR than “standard” PBx (50.5 vs 29.5%; p = 0.002) and such advantage was even greater for clinically significant PCAs (43.9 vs 18.1%; p < 0.001).

In the setting of first PBx, our overall CDR was 76% in Group A and 31.9% in Group B (p = < 0.001) whereas the rate of csPCa was 34.7% in Group A and 18.6% in Group B (p = 0.08), thus similar to that achieved by Porpiglia et al. 7. In the setting of repeat PBx, the overall CDR was 47.1% in Group A and 26.9% in Group B (p = 0.032) whereas the rate of csPCa was 18.8% in Group A and 8.9% in Group B (p = 0.132). Our complication rate was low and consisted of minor events: however, all complications occurred in patients > 75y suffering several comorbidities.

A potential limitation is not having planned a comparison with other tools that have been reported to predict PBx outcome. A commercially available assay combining serum PSA with urinary prostate cancer antigen 3 (PCA3) and the urinary transmembrane protease, serine 2:v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2: ERG fusion) has been shown to provide a 90% specificity and 80% sensitivity in diagnosing PCa.21. Similarly, we demonstrated that, in a small cohort of 40 patients scheduled for repeat PBx, Pentraxin 3 significantly outperformed PSA (AUC 0.92 vs 0.55) in predicting the risk of being diagnosed with PCa.22. These findings, however, await validation in a large series of patients scheduled for first PBx. Another front of research has been addressed towards readily available clinical parameters related to benign prostatic obstruction (BPO). Prostate volume, which is directly correlated to BPO, has been shown to be inversely correlated with the risk of harboring PCa in men scheduled for PBx.23 24. Being in line with this, we found that, in patients scheduled for PBx because of increased PSA levels and/or abnormal DRE, the International Prostate Symptom Score (IPSS), the peak flow rate (PFR) and the post-void residual (PVR) independently predict the risk of being diagnosed with PCa.25-27. A novel nomogram based on BPO-related parameters (PFR, PVoI, PVR) has recently been shown to predict the risk of prostate cancer at first prostate biopsy with a model predictive accuracy of 0.768 for overall PCa and of 0.8002 for Clinical significant PCa.28.

Question remains whether such clinical factors may impact on the treatment outcome, like smoke in bladder cancer and this is particularly true in elderly patients who present several comorbidities.29.

In conclusions, mpMRI/TRUS fusion-guided PBx provided greater CDR than standard TRUS-guided systematic PBx in the setting of first and repeat PBx. Increasing the CDR of PBx would significantly reduce the number of unnecessary PBxs with significant benefits in terms of costs and patient anxiety. On the other hand, one should take into account the risk of overdiagnosing low-risk PCa, with overtreatment possibly leading to procedure-related complications.30. Therefore, like for other common benign urological conditions, the final clinical decision has to rely on wise clinical judgment.31-33.

Acknowledgements

We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

Conflict of interest

The authors declare no conflict of interest.

References

1 Liss MA, White NS, Parsons JK, et al. MRI-derived restriction spectrum imaging cellularity index is associated with high grade prostate cancer on radical prostatectomy specimens. Front Oncol 2015;15:30-6.


Combined peri-anal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy. BJU Int 2012;109:1776-80.


Kobayashi T, Mitsuorni K, Kawahara T, et al. Prostate gland volume is a strong predictor of biopsy results in men 70 years or older with prostate-specific antigen levels of 2.0-10.0 ng/mL. Int J Urol 2005;12:969-75.


Prostate cancer detection rate of multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy. Impact of clinical indications on biopsy outcome

G. Silecchia¹, O. Selvaggio¹, P. Milillo², A. Tewari³, G. Stallone⁴, G. Carrieri¹

¹ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Department of Radiology, University of Foggia, Italy; ³ Department of Urology, Mount Sinai School of Medicine, New York, USA; ⁴ Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy.

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed. The median age at diagnosis is 66y; though many elderly men who are diagnosed with PCa will die from other causes, 70% of deaths occur in men older than 75y. Moreover, elderly patients are more likely than younger patients to be diagnosed with aggressive cancers. Therefore, early diagnosis of PCa in the elderly represents a relevant clinical issue.

Background & Aims. Multiparametric Magnetic Resonance Imaging has increased our ability to diagnose prostate cancer but questions remain about its proper use. Herein we evaluated potential differences between the clinically and multiparametric Magnetic Resonance Imaging-indicated and the non-clinically but multiparametric Magnetic Resonance Imaging-indicated fusion prostate biopsy.

Methods. Outcomes of 99 fusion prostate biopsies (Group A) were compared with those of a matched population having undergone standard prostate biopsy (Group B).

Results. The overall cancer detection rate was 60.6% in Group A and 29.2% in Group B (p < 0.001) whereas the rate of clinically-significant prostate cancer was 26.2% in Group A and 13.1% in Group B (p = 0.02). The cancer detection rate was 79.1% vs 13.1% for clinically-indicated and non clinically-indicated fusion biopsies, respectively; the clinically significant prostate cancer rate in these 2 populations were 45.6 and 0%, respectively. Cancer detection rate correlated with the Prostate Imaging-Reporting and Data System; in the setting of first biopsy, it was 84.6, 67.8%, and 100% for score 3, 4 and 5, respectively, whereas in the setting of repeat biopsy it was 28.5, 55.5% and 80% for score 3, 4 and 5, respectively. Complications rate was similar in both groups but all complications occurred in patients > 75y.

Conclusions. Fusion prostate biopsy provided better cancer detection rate than standard prostate biopsy providing proper clinical indications. The misuse of multiparametric Magnetic Resonance Imaging in patients with no clinical indication for prostate biopsy led, particularly in the elderly, to an extremely high number of unnecessary biopsies with their inherent problems.

Key words: Prostate Cancer, Magnetic Resonance Imaging, Fusion biopsy, Systematic biopsy, Detection rate
an elevated serum PSA level and/or an abnormal digital rectal examination (DRE) is in the range of 40% \(^6\), dropping to approximately 25% in the setting of screening programs, i.e. patients with serum PSA between 2.5 and 10 ng/mL \(^7\).

In the last 20 years, efforts to improve the diagnostic yield of PBx have been oriented towards the construction of predictive models combining serum PSA and DRE findings with other readily available clinical information such as age, prostate volume (PVol), %free PSA etc., as well as towards the development of novel biomarkers \(^8\) or imaging techniques. Among imaging techniques, multiparametric magnetic resonance imaging (mpMRI) of the prostate is increasingly been used given its postulated ability to identify lesions at high-risk of being clinically significant cancers, to improve PBx diagnostic yield by fusion of mpMRI and transrectal ultrasound (TRUS) images, and to increase the accuracy of models predicting PBx outcome \(^9\).

The optimal clinical application of mpMRI, however, remains under investigation. According to current EAU guidelines \(^10\), despite the use of the new PIRADS v2 scoring system, mpMRI has a low specificity, with high rates of false positives, especially among lesions scored 3/5 and 4/5. Moreover, the inter-reader reproducibility is moderate, limiting its broad use outside expert centres. Having said this, EAU guidelines recommend it before repeat biopsy (evidence level 1\(^°\); grade A).

In clinical practice, however, clinicians have to face two different problems. On one hand, there is a certain reluctance to advise PSA testing in men > 75y as well as to recommend prostate biopsy (PBx) for increased PSA levels, particularly in elderly men with PSA in the grey zone (4-10 ng/ml) who suffer from lower urinary tract symptoms (LUTS). On the other hand, the increasing use of prostate mpMRI is leading to indicating PBx on the basis of this exam only, thus independently on clinical indications.

In this study we compared the outcome of mpMRI/TRUS fusion-guided PBx with that of “standard” systematic TRUS guided PBx and evaluated potential outcome differences between the clinically and mpMRI-induced (CI) and the non-clinically but mpMR-induced (NCI) fusion PBxs.

**Patients and Methods**

Data of patients scheduled for TRUS-guided transrectal PBx because of increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE) were prospectively entered into our dedicated Institutional Review Board-approved database. In the present study we compared the first 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) with a matched population of patients having undergone standard TRUS-guided PBx (Group B) in the same period.

MpMRI was carried out using Intera Achieva by Philips with 1.5 tesla magnetic field strength, in T2WI, DWI axial at 3 b values and DCE-MRI (3Dt1W-THRIWE). PBx was carried under local non-infiltrative anaesthesia \(^11\) \(^12\). TRUS was used to determine prostate and transition zone volume and to guide transrectal prostate sampling according to our systematic 18-core biopsy scheme \(^13\). In Group A, care was taken to identify the position of the index lesion(s) within our 18-core scheme and to take 2 cores from it using the Navigo™ Workstation (UC-CARE Medical System).

Two senior uropathologists blind to procedural data evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) \(^14\) of prostate, and PCa.

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

**Statistical Analysis**

Continuous variables were compared by the Mann-Whitney U-test. Rates were tested by the Fisher’s exact test or the chi-square test, as appropriate. Statistical significance was set at p < 0.05. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

**Results**

Table I reports the baseline characteristics of the 99 patients having undergone mpMRI/TRUS fusion-guided PBx (Group A) and those of a matched population of patients having undergone standard systematic TRUS-guided PBx (Group B). The percentage of patients aging > 75y was 20.2% (20/99). Procedural time was 37 ± 5.1 min in Group A and 11 ± 1.7 min in Group B (p < 0.001); there was no difference in complications rate (Group A 4% vs Group B 3%), but all complications occurred in patients > 75y. The overall CDR (Tab. II) was 60.6% in Group A and 29.2% in Group B (p < 0.001) whereas the rate of clinically-significant PCAs (csPCa), defined as cancers with Gleason sum ≥ 7 \(^15\), was 26.2% in Group A and 13.1% in Group B (p = 0.02). In Group B, all PBxs were CI (elevated/raising PSA level and/or an abnormal DRE). In Group A, conversely, 72 PBxs were mpMRI and CI,
whereas 27 were mpMRI but NCI In the CI PBxs, the overall CDR was 79.1% as opposed to 11.1% in the NCI (p = 0.0001); the rates of csPCAs in these 2 populations were 45.6 and 0%, respectively (p = 0.0001). Of the 27 patients having a NCI PBx, 9 (33.3%) were > 75y.

CDR correlated well with the Prostate Imaging-Reporting and Data System (PIRADS), being 50%, 61.8% and 90% for PIRADS 3, 4 and 5, respectively in the overall population, and 78.9, 75 and 100% for PIRADS 3, 4 and 5, respectively in the CI PBxs (Tab. III).

**DISCUSSION**

The identification of factors that could predict PBx outcome is of major clinical importance. Rising the CDR of PBx would significantly reduce the number of unnecessary PBxs, in other words those that are likely to result negative for PCa, with a significant reduction in costs and patient anxiety.

A commercially available assay combining serum PSA with urinary prostate cancer antigen 3 (PCA3) and the urinary transmembrane protease, serine 2:v-ets erythroblastosis virus E26 oncogene homolog (TMPRSS2:ERG fusion) has been shown to provide a 90% specificity and 80% sensitivity in diagnosing PCa. Similarly, we demonstrated that, in a small cohort of 40 patients scheduled for repeat PBx, Pentraxin 3 significantly outperformed PSA (AUC 0.92 vs 0.55) in predicting the risk of being diagnosed with PCa; these findings, however, await validation in a large series of patients scheduled for first PBx.

Another front of research has been addressed towards readily available clinical parameters related to benign prostatic obstruction (BPO). Prostate volume, which is directly correlated to BPO, has been shown to be inversely correlated with the risk of harboring PCa in men scheduled for PBx. A novel nomogram based on BPO-related parameters (PFR, PVol, PVR) has recently been shown to predict the risk of prostate cancer at first prostate biopsy with a model predictive accuracy of 0.768 for overall PCa and of 0.8002 for clinical significant PCas. Question remains whether such clinical factors may impact on treatment outcome, like smoke in bladder cancer.

In the field of imaging, mpMRI certainly represents the most promising technique in identifying neoplastic prostate lesions that should be sampled. The initial and
simplest MRI-targeted biopsy strategy is the cognitive approach. Three RCTs have compared a TRUS-guided 12-core PBx with a cognitive mpMRI-guided PBx in the setting of first PBx yielding conflicting results. 25-27. The first two studies pointed out that CDR was higher in the mpMRI-guided group 26 27, whereas the most recent one showed that the two procedures provided comparable results (25).

The mpMRI/TRUS fusion software has been developed with the aim of providing a more precise sampling of the lesions identified by mpMRI. Initial non-randomized studies comparing mpMRI/TRUS fusion PBx with “standard” TRUS-guided PBx in the setting of first PBx pointed out that fusion PBx provided better CDR than “standard” PBx 28 29.

The first RCT comparing mpMRI/TRUS fusion guided PBx with “standard” 12-core TRUS-guided PBx in the setting of first PBx 15 pointed out that “fusion” PBx provided a significantly greater overall CDR than “standard” PBx (50.5 vs 29.5%; p = 0.002) and such advantage was even greater for clinically significant PCas (43.9 vs 18.1%; p < 0.001). Such results can however be expected after having completed the learning curve of both radiologists and urologists with this procedure. Panebianco et al. 27 reported a learning curve of approximately 50 cases whereas Calio et al. 19 reported a learning curve of 270 cases.

Findings of the present study were clear. In matched populations, fusion PBx provided greater CDR than standard systematic PBx for overall PCa and csPCa. The novel and strong point of our study was assessing the impact of mpMRI on indications for PBx. A relevant (27%) number of patients had to undergo fusion PBx only on the basis of mpMRI results; in other words, PBx was mpMRI-indicated but NCI. This led to a disastrous 11.1% CDR, therefore, a huge number of unnecessary PBxs with all their burden in costs, risks, and patients anxiety. On the other hand, and this can be considered another strong point of our study, CI fusion PBxs yielded a very satisfactory 78.9, 75 and 100% CDR for PIRADS 3, 4 and 5, respectively. These findings somehow challenge the reported mpMRI low specificity and high rates of false positives among PIRADS 3 and 4 lesions 30.

It is worth mentioning that in Group A the percentage of patients aging > 75y was 20.2%, much higher than our historical 12% rate. Moreover, 33.3% of patients who had a NCI fusion PBx were > 75y. Overall, these findings suggest that potential misuse of fusion PBx is more likely to occur in the elderly. This is even more troublesome in view of the fact that complications, though always minor, were all seen in patients > 75y. The main study limitation is the relatively small number of patients. Though case volume is known to play a relevant role in surgical procedures 31, the number of enrolled patients appeared to be sufficient to provide relevant information on performance and trend of use of this novel procedure particularly in the elderly population. In conclusions, mpMRI/TRUS fusion-guided PBx had greater CDR than standard TRUS-guided systematic PBx providing correct clinical indications. Clinicians, however, have to face the problem of inappropriate use of this imaging technique (NCI cases) resulting into an increase rather than a decrease in the number of unnecessary PBxs exposing patient to the risk of over-diagnosis and consequent overtreatment with possible procedure-related complications 32. Interestingly, elderly patients seemed to be those at higher risk of undergoing a NCI fusion PBx. Like for other common benign urological conditions, wise clinical judgment remains essential in the decision-making process 33-35.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


**Table III. Cancer detection rate by prostate imaging-reporting and data system (PIRADS) scores in patients having undergone mpMRI/TRUS fusion-guided PBx.**

<table>
<thead>
<tr>
<th>Group A</th>
<th>PIRADS 3, % (n)</th>
<th>PIRADS 4, % (n)</th>
<th>PIRADS 5, % (n)</th>
<th>Overall, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All pts (99)</strong></td>
<td>50 % (17/34)</td>
<td>61.8 % (34/55)</td>
<td>90 % (9/10)</td>
<td>60.6 % (60/99)</td>
</tr>
<tr>
<td><strong>CI pts (72)</strong></td>
<td>78.9 % (15/19)</td>
<td>75 % (33/44)</td>
<td>100 % (9/9)</td>
<td>79.1 % (57/72)</td>
</tr>
<tr>
<td><strong>NCI pts (27)</strong></td>
<td>14.2 % (2/14)</td>
<td>9 % (1/11)</td>
<td>0 % (0/2)</td>
<td>11.1 % (3/27)</td>
</tr>
</tbody>
</table>

**Notes:**

- The Cancer detection rate by prostate imaging-reporting and data system (PIRADS) scores in patients having undergone mpMRI/TRUS fusion-guided PBx.
- Group A CI pts (72) and Group A NCI pts (27) refer to the specific groups within the overall population.
Prostate cancer detection rate of multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy

4 Ko J, Falzarano SM, Walker E et al. Prostate cancer patients older than 70 years treated by radical prostatectomy have higher biochemical recurrence rate than their matched younger counterpart. Prostate 2013;73:897-903.


SHORT COMMUNICATION

A lycopene and olives vegetation water compound improves lower urinary tract symptoms in men with histologically-proven benign prostatic hyperplasia and inflammation

G. Silecchia¹, O. Selvaggio¹, E. Barret², F. Sanguedolce³, G. Stallone⁴, L. Cormio¹

¹ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Department of Urology, Institut Montsouris, Paris, France; ³ Section of Pathology, Department of Clinical and Experimental Medicine, University of Foggia, Italy; ⁴ Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease widely diffused between the elderly population. Indeed, its incidence increases with age, reaching 80% of males aging 70 to 80 years¹. It develops as a simple micronodular hyperplasia and then progress to macroscopic volume enlargement and clinical expression. There is emerging evidence that prostatic inflammation plays a key role, since BPH evolves through early and late inflammatory modifications. Indeed, the prostate is an immunocompetent organ populated by T and B-lymphocytes, macrophages and mast cells². Regulatory T cells (CD-4) are located into the fibromuscolar stroma whereas Cytotoxic T cells (CD-8) are more distributed around periglandular area creating the so-called Prostate associated Lymphoid Tissue (PALT). There are two main clinical manifestations of prostatic

Background and aims. There is evidence for the ability of antioxidants to counteract the effects of inflammation. We aimed to determine whether the administration of a lycopene/olives vegetation water compound might reduce prostatic inflammation and consequent lower urinary tract symptoms in patients with histologically proven prostatic inflammation.

Methods. Over a month period, patients having undergone prostate biopsy and having been diagnosed with benign prostate were given lycopene/olives vegetarian water compound (Group A). Data were compared with those of a matched population of patients who did not receive such treatment (Group B). International prostate symptom score, peak flow rate and post-void residual were recorded before and at the end of treatment.

Results. The 17 patients in group A and the 17 in group B, had similar age, PSA, prostate volume, peak flow rate and post-void residual, but patients in Group A had lower median international prostate symptoms score than those in group B (7 vs 12; p = 0.012). All patients in group A successfully completed treatment with no side effect. Group B experienced no difference in international prostate symptoms score, peak flow rate and post-void residual whereas group A experienced no difference in peak flow rate, a slight reduction in post-void residual and a decrease in international prostate symptoms score. Most important, reduction in international prostate symptoms score was significantly higher in group A than in group B (-2.0 vs 0, respectively; p = 0.0004).

Conclusions. The lycopene/olives vegetation water compound seems to be effective in counteracting lower urinary tract symptoms due to prostatic inflammation.

Key words: Lycopene, Olives vegetation water, Prostatic inflammation, LUTS, Benign prostatic Hyperplasia
inflammation, namely lower urinary tract symptoms (LUTS) and increase in serum PSA often leading to prostate biopsy (PBx).

Data suggest that a potential mechanism by which inflammation promotes prostate enlargement is local hypoxia, which is responsible for the release of reactive oxygen species (ROS). Such ROS promote neovascularization and further release of vascular endothelial growth factors (VEGFs), interleukin-8 (IL-8), fibroblast growth factor 7 (FGF-7), transforming growth factor (TGF-b), and fibroblast growth factor (FGF-2). All of them contribute to prostatic enlargement and further inflammation.

There is also evidence that, apart from promoting prostatic enlargement, prostatic inflammation may also promote prostate cancer (PCa). Like BPH, PCa is common among elderly males. The median age of PCa diagnosis is 66 years, and nearly 20% of patients are diagnosed when they age 75y or more. The immune cells can stimulate tumor cell proliferation and angiogenesis by the production of reactive oxygen species and by inflammatory processes that result into tissue damage and permanent DNA damage.

A recent meta-analysis, however, pointed out that the presence of inflammation on prostate needle biopsy was associated with a lower PCa risk.

In the absence of a standard treatment for prostatic inflammation, the use of substances like antioxidants that may stop or potentially reverse the deleterious effects of inflammation is particularly attractive. Lycopene and olives vegetation water are well-known strong antioxidants, with properties potentially useful in protecting DNA from oxidation.

The present study therefore aimed to determine whether the administration of a lycopene and olives vegetation water compound might reduce inflammation and therefore LUTS in patients with histologically proven prostatic inflammation.

PATIENTS AND METHODS

Over a one-month period, consecutive patients having undergone prostate biopsy (PBx) at our institution and having been diagnosed with benign prostate were given lycopene/olives vegetable water compound (Group A). Data were compared with those of a matched population of patients having undergone prostate biopsy and having been diagnosed with benign prostate (Group B). All data were prospectively entered into our dedicated Institutional Review Board-approved database on prostate biopsy.

Indications for trans-rectal ultrasound (TRUS)-guided PBx were increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE). All patients underwent International prostate symptom score (IPSS) and uroflowmetry (UFM) before PBx, as we have demonstrated that BPO-related parameters such as peak flow rate (PFR), post-void residual (PVR) and IPSS are independent predictors of the risk of being diagnosed with PCa. Recently, we also developed a novel BPO-related parameters nomogram that may help reducing the number of unnecessary PBxs, thus reducing the risk of over diagnosis and consequent overtreatment with possible procedure-related complications. Following local non-infiltrative anaesthesia, TRUS was used to determine prostate and transition zone volume and to guide trans-rectal prostate sampling according to our systematic 18-core biopsy scheme. A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate and PCa.

Patients in group A, unless reporting a history for allergies or hypersensitivity to tomato, inflammatory diseases of the urogenital tract (i.e. orchitis, epididymitis or both) and malabsorption syndrome, were given lycopene/olives vegetable water compound in the form of 5 gr medical bags to be dissolved in water or other liquid once-a-day for 2 months. The intake could take place before, during or after meals. Patients in Group B did not receive any treatment. All patients were seen after 2 months for IPSS questionnaire, clinical evaluation and uroflowmetry to assess PFR and PVR.

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

Statistical analysis

The primary study endpoint was assessing changes in IPSS, PFR and PVR; the secondary endpoint was to assess safety.

Continuous variables are reported as median and interquartile range; they were compared by the Mann-Whitney U-test. Rates were tested by Fisher’s exact test or chi-square test, as appropriate. Statistical significance was set at p < 0.05. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

Results

The study population consisted of 34 patients, 17 in Group A and 17 in Group B; their characteristics are summarized in Table I. Overall, the two groups had similar age, PSA, prostate volume (PVol), PFR and PVR.
but patients in group A had lower median IPSS score than those in group B (7 vs 12; \( p = 0.012 \)).

All patients in group A successfully completed treatment with no side effect. Patients in group B experienced no difference in their median PFR and PVR (Tab. II) but a slight increase in median IPSS, which might however be due to the impact of the procedure itself on voiding symptoms. Patients who received the lycopene/olives vegetation water compound (Group A), experienced no difference in their median PFR, a slightly lower PVR and, above all, a decrease in their median IPSS. Comparing the two groups, median reduction in IPSS was significantly higher in group A than in group B (-2.0 vs zero, respectively; \( p = 0.0004 \)).

DISCUSSION

The present study pointed out that, in men with histologically-proven prostatic inflammation and benign prostate, the administration of a lycopene/olives vegetation water compound after PBx provided a statistically significant reduction in IPSS as compared to no treatment. In both groups, there was no significant change in PFR, but patients in group A experienced a slight reduction in their PVR. These findings would support a role for the lycopene/olives vegetation water compound in reducing prostatic inflammation and consequent LUTS.

The correlation between prostatic inflammation and LUTS has been strongly pointed out by Nickel et al. who evaluated 8224 men aged 50-75 years with BPH undergoing prostate biopsy and included in the REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial. Patients were classified according to the presence of acute and chronic inflammation at biopsy. Interestingly, 77.6% of patients presented with chronic inflammation. These patients had higher prostate volumes than those without inflammation (46.5 vs 43.4 mL, respectively; \( p < 0.001 \)). Interestingly, older age and higher degree of chronic inflammation were significantly associated with higher IPSS (8.8 vs 8.2, respectively; \( p < 0.001 \)), particularly the storage IPSS sub-scores (frequency, nocturia, urgency). Similarly, Robert et al. found, in 282 patients treated with surgery for complicated or symptomatic BPH, that the grade of prostatic inflammation was strongly associated with LUTS severity, and patients with chronic inflammation had higher IPSS than those without inflammation (21 vs 12, respectively; \( p = 0.02 \)).

Counteracting inflammation is relevant not only to reduce symptoms but also to slowing development and progression of BPH. Indeed, Tuncel et al. have shown that the presence of prostatic inflammation is a risk factor for the development of BPH complications such as acute urinary retention. The Medical Therapy of Prostatic Symptoms (MTOPS) study, whereby 3000 patients with LUTS due to BPH were treated for 5 years, highlighted that the percentages of disease progression, urinary retention and need for surgery were higher in patients with chronic inflammatory status than in those without it. It has also been pointed out

**Table I. Patients baseline characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Group A = 17</th>
<th>Group B = 17</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>67.0 (63.0, 70.0)</td>
<td>65.5 (62.5, 67.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>PSA (ng/mL)*</td>
<td>7.3 (5.2, 11.7)</td>
<td>5.6 (4.7, 7.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Prostate volume (mL)*</td>
<td>55.0 (50.0, 66.4)</td>
<td>60.0 (50.0, 85.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>IPSS*</td>
<td>7.0 (5.0, 12.0)</td>
<td>12.0 (9.0, 16.0)</td>
<td>0.012</td>
</tr>
<tr>
<td>PFR (mL/s)*</td>
<td>14.4 (11.0, 17.7)</td>
<td>14.9 (12.7, 17.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>PVR (mL)*</td>
<td>35.0 (0.0, 50.0)</td>
<td>35.0 (0.0, 45.0)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Data are expressed as median and Interquartile range.

**Table II. Treatment outcomes.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A = 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS*</td>
<td>7.0 (5.0, 12.0)</td>
<td>4.0 (3.0, 9.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>PFR (mL/s)*</td>
<td>14.4 (11.0, 17.7)</td>
<td>14.4 (12.4, 19.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>PVR (mL)*</td>
<td>35.0 (0.0, 50.0)</td>
<td>28.5 (0.0, 41.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Group B = 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS*</td>
<td>12.0 (9.0, 16.0)</td>
<td>14.0 (9.0, 16.0)</td>
<td>1</td>
</tr>
<tr>
<td>PFR (mL/s)*</td>
<td>14.9 (12.7, 17.3)</td>
<td>14.1 (11.6, 17.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>PVR (mL)*</td>
<td>35.0 (0.0, 45.0)</td>
<td>35.0 (15.0, 50.0)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Data are expressed as median and Interquartile range.
that, like smoking in bladder cancer, inflammation has a negative impact on response to conventional BPH treatments. Therapy such as alpha-blockers and 5-alpha reductase inhibitors.

The clinical relevance of prostatic inflammation and consequent LUTS is further highlighted by the fact that LUTS and cardiac symptoms have the same impact on the general state of health and quality of life. Counteracting inflammation could be relevant to reduce the risk of developing PCAs. If it is true that inflammation on prostate needle biopsy is associated to benign prostate more frequently than to PCA risk, it is also true that several studies support the role of chronic inflammation in malignant transformation. Interleukin (IL)-8 and IL-6 have been reported to promote PCa. A recent preclinical investigation showed that IL-17 might promote the development of PCa through the activation of the matrix metalloproteinase-7 expression. A large prospective study on 68,675 patients demonstrated that a personal history of prostatitis, as well as symptom duration, were significantly associated with an increased risk of PCa.

While searching for novel molecular markers and pathways potentially involved in prostatic inflammation, up to representing potential therapeutic targets, the main issue remains what do we already have to counteract inflammation. ROS involvement in prostatic inflammation make antioxidants an attractive means of counteracting them. Indeed, lycopene is a powerful antioxidant with proven anti-inflammatory effect. Pannellini et al. showed that tomato-based preparations optimized to maximize lycopene and other carotenoids bioavailability were able to significantly increase the antioxidant serum activity and, at the same time, to reduce biomarkers inflammation in the mouse TRAMP. Another interesting antioxidant is 3,4-dihydroxyphenyl ethanol or hydroxytyrosol (HT), a simple phenol predominantly found in Olea europea also known as the olive plant. Specifically, HT is most abundant in the aqueous fraction of olive pulp with trace amounts in the olive oil fraction and in the leaves. Olive vegetation water and HT have been found to exploit anti-inflammatory activity in mice by inhibiting the production of tumor necrosis factor-alpha (TNF-alpha), a pivotal cytokine in inflammation. Our findings of a relatively short course of these two substances reducing IPSS seem to provide a proof of concept for their effect against prostatic inflammation. This study is not devoid of limitations. One is the small patients’ number but this aimed to be a pilot study in this field. Others include the relatively short time-frame of treatment and the absence of another control group receiving other substances potentially active against prostatic inflammation, but again this was beyond the scopes of a small pilot study.

In conclusion, there seems to be a clear link between prostatic inflammation, BPO and LUTS. In view of the postulated immunocompetent nature of the prostate, modulators of the immune response, which are opening new pathways in several urological cancers, are attractive but probably too costly. Antioxidants conversely stand as a potential simple means of counteracting prostatic inflammation and this small study seems to be a proof of such concept.

**CONFICT OF INTEREST**

The authors declare no conflict of interest.

**References**

A lycopene and olives vegetation water compound improves lower urinary tract symptoms in men...


Hemostatic sealant in tubeless percutaneous nephrolithotomy: a monocentric experience

M. Auciello1, A. Mangiatordi1, G. Stallone2, G. Carrieri1, A. Hoznek3, L. Cormio1

1 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 2 Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 3 Department of Urology, Henri Mondor Hospital, Créteil, France

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the recommended treatment option for large or otherwise complex renal or proximal ureteral stones. Since first described by Fernstrom and Johannson 1, great efforts have been made to improve the outcomes of this surgical procedure by optimizing its surgical steps, including patient positioning, puncture of the collecting system, dilation and fragmentation modality, and exit strategy 2. The latter remains an area of continuing innovation and debate due to its relevant impact on postoperative clinical outcome.

The practice of routine placement of a large bore (20 to 26Fr) nephrostomy tube (NT), traditionally recommended to achieve hemostasis, urinary drainage and access for a second look procedure, has been challenged since the early 1980s 3 but the concept of “tubeless” PCNL remained neglected until 1997, when Bellman et al. 4 demonstrated that placement of a Double-J stent instead of a NT was associated with less postoperative pain, decreased analgesia requirement, shorter hospital stay and stone-free rate.

Background and aims. Tubeless percutaneous nephrolithotomy is increasingly been used but the question remains on the wisdom of using an hemostatic agents to seal the tract and whether this decision should be based on tract size. We compared the outcome of standard (26-30Fr) tubeless percutaneous nephrolithotomy sealed with Tachosil® vs mini (17.5Fr) percutaneous nephrolithotomy with a tract left unsealed.

Methods. We analysed our prospectively maintained Internal Review Board-approved percutaneous nephrolithotomy database to compare outcomes of patients who had undergone tubeless percutaneous nephrolithotomy either sealed or unsealed.

Result. Among 491 eligible patients, 294 had a mini (17.5 Fr) unsealed (Group A) and 197 a standard (26-30 Fr) sealed procedure (Group B). Groups were similar for baseline characteristics but median surgical time was significantly shorter (60 vs 75 min; \( p = 0.0004 \)) in unsealed rather than in sealed procedures. There was no difference in the overall complications rate (44.9 vs 39.1%, \( p = 0.2 \)); median Hb loss was statistically lower (0.8 vs 1.0; \( p = 0.028 \)) in unsealed procedures but there was no difference in blood transfusion rate (3.1 vs 3.6%; \( p = 0.8 \)). Four patients required embolization, 3 (1%) in unsealed and 1 (0.5%) in sealed procedures; 4 had urinary leakage from the flank requiring ureteral stenting, 3 (1%) in unsealed and 1 (0.5%) in sealed procedures. Finally, there was no difference in mean postoperative hospital stay and stone-free rate.

Conclusions. Tubeless percutaneous nephrolithotomy were proved to be safe, but elderly patients deserve more attention. The use of sealants, while not always necessary, may be useful in optimizing results.

Key words: Percutaneous nephrolithotomy, Sealant, Urolithiasis
stay and faster return to normal activities. Several studies subsequently confirmed the tubeless approach to be associated with reduced postoperative pain and hospital stay. Nevertheless, the wisdom of tubeless PCNL continues to be challenged by studies demonstrating the advantages of early NT removal or placement of small bore NTs over the tubeless approach. Indeed, most endourologists continue to favor NT placement probably due to fear of bleeding or urinary leakage through a tract left open, particularly in the elderly population whereby the healing process is expected to be less effective.

Hemostatic agents appear to be an attractive means of sealing the tract without using a tube; again, this option could be most useful in the elderly. Indeed, sealed tubeless PCNL has been suggested to reduce patient discomfort and urinary leakage compared to unsealed tubeless PCNL or NT placement but if and which agent should be used remain controversial. We demonstrated that TachoSil® Sealed Tubeless PCNL provided better tract control and a shorter hospital stay than NT placement in patient having undergone standard PCNL (30Fr Amplatz sheath). Others suggested the use of sealants also when using a smaller percutaneous access (mini-PCNL) but the minimal invasivity and, consequently, the theoretically minimal parenchymal trauma of mini-PCNL would question the need for sealants during PCNL.

The present study aimed to compare the outcome of standard (26-30Fr) tubeless percutaneous nephrolithotomy with TachoSil® vs mini (17.5Fr) percutaneous nephrolithotomy with a tract left unsealed. Special attention was given to the elderly population.

PATIENTS AND METHODS

Data of patients scheduled for PCNL at our Department were prospectively entered into our Internal Review Board approved dedicated database. Preoperatively, all patients underwent abdominal computed tomography scanning and urine culture. Antibiotic prophylaxis was carried out according to current recommendations. All procedures were carried out in our supine antero-lateral position or in the Galdakao-modified supine position. Until the end of 2014, standard anesthesia was general whereas, from the beginning of 2015, it was spinal. Renal collecting system was punctured under fluoroscopic guidance using an 18G needle. The percutaneous tract was dilated to 26-30F (standard PCNL) or, by the beginning of 2014, to 17.5F (mini-PCNL). Following stone/s fragmentation/extraction, flexible ureteroscopy and/or nephroscopy was carried out to check for stone clearance. Whenever possible, the procedure was closed placing a mono-J ureteral stent and a Foley catheter, thus were tubeless or TachoSil®-sealed tubeless procedures. Whenever deemed necessary, we used a double-J stent instead of the mono-J ureteral catheter or a nephrostomy tube. All procedures were carried out by one of us (LC).

All patients underwent abdomen X-ray and renal ultrasound (US) at 1 month postoperatively to assess stone free rate (SFR). Abdominal CT was used as needed. Patients with residual fragments ≤ 4 mm were considered stone-free. Perioperative complications were assessed using the Clavien classification system adjusted for PCNL. Infective complications were defined fever > 38°C or SIRS lasting > 24h, and/or infection of urine of blood.

STATISTICAL ANALYSIS

The Mann-Whitney U-test was used for continuous variables, whereas the Chi-square test was used for categorical variables. Data were analysed by Stata 14 (StataCorp LP, College Station, TX, USA). All tests were 2-sided with a significance level set at p < 0.05.

RESULTS

Between April 2005 and March 2018, a total of 491 patients underwent tubeless PCNL at our Institution. Among them, 294 had a mini (17.5 Fr) unsealed (Group A) and 197 a standard (26-30 Fr) sealed procedure (Group B). Patients baseline characteristics are summarized in Table I. Basically, there was no difference in age, gender, body mass index (BMI), American Society of Anesthesiologists Classification (ASA score), positive preoperative urine culture rate, and stone features. However, mean stone size in patients with single or multiple stones was smaller in Group A. Median surgical time was significantly shorter in unsealed than in sealed PCNLs (60.0 [IR 50.0, 90.0] vs 75.0 [IR 60.0, 100.0], respectively; p = 0.0004). There was no difference in the positive stone culture rate (10.8 vs 17.6%; p = 0.1).

Table II summarizes outcomes. There was no difference in the overall complications rate (44.9% vs 39.1%, p = 0.2) nor in the different grades of Clavien scores. Median Hb loss was statistically lower (0.8 vs 1.0; p = 0.028) in unsealed than in sealed procedures, but there was no difference in blood transfusion rate (3.1 vs 3.6%; p = 0.8). Indeed, 4 patients required embolization due to postoperative bleeding, 3 (1%) in the unsealed and 1 (0.5%) in the sealed procedures. Urinary leakage from the flank lasting > 12h, thus requiring placement of a double-J stent, occurred in 4 patients, 3 (1%) in the unsealed and 1 (0.5%) in the sealed procedures. Finally,
there was no difference in mean postoperative hospital stay, infective complication and stone-free rate.

Table III reports the outcomes of patients > 70y. There was no difference in the overall complications rate nor in the different grades of Clavien scores. Specifically, there was no difference in blood transfusion rate (7.1 vs 4%) nor in the infective complications rate (7.1 vs 12%). Having said this, it is worth mentioning that the blood transfusion rate of elderly patients who had an unsealed procedure was double that of their younger counterpart (7.1 vs 3.1%; p = 0.1790). Also the infective complications rate was higher in the elderly as opposed to their younger counterpart (7.1 vs 2.7% for unsealed procedures, p = 0.1466; 5.1 vs 12% for sealed procedures, p = 0.1685).

**DISCUSSION**

TachoSil® is a sterile, ready to use absorbable patch consisting of an equine collagen matrix coated with fibrin glue components, human fibrinogen and human thrombin, thus combining the assets of a pliable patch material with the hemostatic and adhesive properties of the coagulation factors. Its efficacy and safety have been demonstrated in several surgical procedures leading to product approval in Europe as a supportive hemostatic treatment for intraoperative topical application. We previously demonstrated 16 that TachoSil® sealed tubeless PCNL provided better tract control and a shorter hospital stay than NT placement in patient having undergone standard PCNL (30Fr Amplatz sheath).
In a recent systematic review and meta-analysis, Yu et al. addressed the use of hemostatic agents for tract closure after tubeless PCNL. Eight studies including six RCTs showed that use of hemostatic agents was safe. Hemostatic agents showed short hospital stay. There were no difference between hemostatic agents and common methods on blood loss, transfusion rate, fever rate, and complication rate. Another recent systematic review and meta-analysis addressing the use of hemostatic agents for tract closure after tubeless PCNL analyzed 7 studies involving 351 patients. Again, hospital stay was shortened in sealed patients than in controls ($p < 0.05$). There were no statistically significant difference in terms of Hb drop, analgesic requirements, and blood transfusion rate. In spite of the advantage in hospital stay, the study concluded that, in view of their cost, hemostatic agents might not be necessary in tubeless PCNL.

The present study pointed out no difference in the overall complications rate. There was a statistically but certainly not clinically significant difference in Hb loss in favor of unsealed procedures; indeed, blood transfusion rate was similar in the two groups. Embolization and urinary leakage requiring placement of a double-J stent were slightly more common (1 vs 0.5% for both events) in unsealed than in sealed procedures. While the first event is probably related to puncture/dilation, urinary leakage is probably related to tract handling. Case volume is too small to draw any definite conclusion but findings would suggest that, in terms of urinary leakage, sealing the tract with TachoSil® performs better than NT placement, as shown in our previous study, as well as than just leaving the tract unsealed. If we join findings from our previous study together with those from the present one, it comes out that our rate of urinary leakage requiring stenting is 6% for standard PCNL with NT placement, as shown in the previous study, 1% for unsealed mini-PCNL and 0.5% for TachoSil®-sealed standard PCNL, somehow pointing out a minimal advantage in sealing the tract.

While potentially advantageous, hemostatics rise concerns about their safety, particularly about their potential antigenicity exposing to the risk of local foreign-body reactions, such as granuloma or abscess formation, and/or systemic hypersensitivity/anaphylactic reactions. Clinical studies seem to rule out the risk of systemic reactions, but little is known regarding local reactions, as the only two studies addressing this issue were both carried out on animal models. This issue would deserve further attention.

Differently from the above-mentioned meta-analyses, we found no difference in hospital stay. This may be due to the fact that we adopted the same protocol in sealed and unsealed PCNL and we had quite similar outcome. An interesting and novel information coming from our study was the sub-analysis of elderly (>$70\text{y}$) patients outcomes. While there was no substantial difference between sealed and unsealed procedures also in this subset of patients, it should be noted that the overall complications rate was higher compared to their younger counterpart. Specifically, the blood transfusion rate of elderly patients who had an unsealed procedure was double than the one of their younger counterpart; the same applied for the infective complications rate, which was higher in the elderly patients independently on whether they had a sealed or an unsealed procedure. Though findings did not reach statistical significance, they suggest the elderly patient to be a bit more frail in this respect.

This study is not without limitations. One is its retrospective nature, but data were prospectively collected. Another aspect is difference in Amplatz sheath size, but this provided furthers insights on its impact on urinary leakage. Further studies addressing the role of TachoSil® when using the same sheath size are awaited.

### Table III. Outcomes in elderly (>70y) patients.

<table>
<thead>
<tr>
<th></th>
<th>Group A = unsealed (n = 42)</th>
<th>Group B = sealed (n = 25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavien, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18 (42.9%)</td>
<td>14 (56.0%)</td>
<td>0.14</td>
</tr>
<tr>
<td>I</td>
<td>15 (35.7%)</td>
<td>4 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (9.5%)</td>
<td>1 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>3 (7.1%)</td>
<td>5 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>2 (4.8%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0 (0.0%)</td>
<td>1 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusions, n (%)</td>
<td>3 (7.1%)</td>
<td>1 (4%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Infective complications, n (%)</td>
<td>3 (7.1%)</td>
<td>3 (12.0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>*Postop. Hosp Stay, days</td>
<td>3.0 (2.0, 5.0)</td>
<td>3.0 (3.0, 7.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stone free, n (%)</td>
<td>33 (80.5%)</td>
<td>15 (60.0%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Data are expressed as median (interquartile range).
In conclusion, tubeless PCNL, both sealed and unsealed, provided a safe and effective means of handling the tract. While the use of an hemostatic agent is not always necessary, it may sometimes be useful in optimizing results thus justifying costs. Due to their slightly higher risk of complications, elderly patients deserve greater attention.

Acknowledgements

We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

Conflict of interest

The authors declare no conflict of interest.

References


Micropapillary bladder cancer, a variant histology of the elderly

F. Sanguedolce¹, A. Cormio², B. Calò³, M. Landriscina⁴, E. Carvalho-Dias⁵, L. Cormio³

¹ Section of Pathology, Department of Clinical and Experimental Medicine, University of Foggia, Italy; ² Department of Biosciences, Biotechnologies and Biopharmaceutics, University of Bari, Italy; ³ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ⁴ Medical Oncology Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ⁵ Urology Department, Hospital de Braga ICVS, University of Minho, Braga, Portugal

Micropapillary bladder cancer is a rare variant of bladder cancer with dismal biological behavior. It most frequently affects the elderly and it is essential to define and report its morphological features at pathology since it demonstrates poor response to conventional treatments. This review aims to systematically explore and critically appraise the current state of the evidence regarding clinical features, pathology issues, prognostic factors and therapeutic perspectives in this difficult and peculiar variant of bladder cancer.

Key words: Bladder cancer, Micropapillary, Elderly

EPIDEMIOLOGY

Micropapillary bladder cancer (MPBC) was first reported in 1994 by Amin et al. ¹ as a histological subtype of urothelial carcinoma (UC) which bears a strong resemblance to analogous neoplasms arising in the ovary and breast. As a rare variant of UC, its incidence has been estimated to represent 0.01-8.2% of all urothelial tumors ¹-⁶. MPBC is more frequent in old men, with a male-to-female ratio of 5-10:1 ¹ ⁴ ⁵ ⁷ ⁸ and a mean age at first diagnosis of 67.6 years. According to a very large cohort of MPBC patients (baseline disease characteristics available for 869 patients, survival data available for 348 patients), median patients age was 69.9 years (58.9-80.9) ⁹. Unfortunately, data on prevalence and mortality in patients > 65 years are not available.

There is no specific risk factor for MPBC, which shares the same risk factors of conventional of transitional cell carcinoma.

PATHOLOGY

Its gross appearance may vary, since it can occur as an exophytic (papillary, polypoid) mass or as a flat lesion (ulcerative or infiltrating), and its size may differ accordingly ⁴. The diagnostic gold standard for MPBC is the detection of its peculiar morphological features at transurethral resection (TUR) biopsy, although the diagnosis is often challenging. Neoplastic cells usually appear as slender delicate papillary projections or small compact infiltrating nests from 4 to 5 cells lacking central vascular cores, floating within clear spaces similar to lymphatic channels due to the production of peritumoral stromal retraction artifacts, thus mimicking angiolymphatic invasion by neoplastic cells ⁵ ⁷ ¹⁵-¹⁷. Such aggregates frequently show peripherally located high-grade nuclei and cytoplasmic vacuoles ⁸ ¹⁸; their inverted cellular polarity might result in apical secretory properties shifting...
to the basal surface of cells, ultimately leading to high
tumor invasion 19-20. Cold cup biopsy may miss a MPBC
invading the muscle layer under the benign surface
epithelium; thus deep biopsies are recommended 11-22.
Urine cytology smears are less informative though sug-
gestive, showing papillary/spheroid aggregates of tu-
mor cells with high nuclear grade along with rare single
cells in a clear background 23. Moreover, urine cytology
is unable to detect neoplastic cells in cases of MPBC
growing under normal mucosa 24.
Most MPBCs are found in association with conven-
tional UC and carcinoma in situ (CIS) 24, as well as with
other variants/histotypes of bladder cancer 3-14. Like
conventional UC, MPBC may be either non-muscle in-
vasive or muscle invasive.

The immunophenotype of MPBC is similar to the one de-
scribed in conventional UC; indeed, neoplastic cells usu-
ally express Cytokeratin 7 (CK7), uroplakin III, CK34E12,
CytoKeratin20 (CK20), Protein63 (P63), thrombomodulin,
and High Molecular Weight Cytokeratin (HMWCK) 25-26.
Therefore conventional immunohistochemical markers
have proven unsuccessful because of low specificity and
sensitivity 24-27. Useful markers in the differential diagnosis
with other malignant neoplasms showing micropapillary
morphology (such as lung, breast, ovary cancers) include
Estrogen Receptor (ER), mammaglobin, Pired Box Gene
8 (PAX8), Thyroid transcription factor 1 (TTF1), Wilms Tu-
mor protein1 (WT1) 1-12. Finally, other prominent features of
MPBC include activation of chromatin-remodeling com-
plex RUVBL1 that may be related to the Epidermal Growth
Factor receptor (EGFR), the luminal molecular sub-type
profile, and downregulation of miR-296 28, the latter sug-
cesting that modulators of immune response may play a
role in this disease like in other urological cancers 29-30.

According to Sangoi et al. 7, the interobserver agree-
ment among uropathologists for the diagnosis of MPBC
(especially “non-classic” forms) is only moderate even
within a large academic center, with an overall concord-
ance kappa score of 0.54. They pointed out It may be
improved by taking into account the size and pattern
of tumor cell aggregates (i.e. small multiple nests within
the same lacunar space vs large branching). Limited
interobserver agreement might also be partly due to
a trend to under- or no- reporting variant histologies
of UC, particularly outside of academic institutions 31,
and partly to sampling error and tumor heterogeneity
as TUR specimens have been reported to detect only
39% of variant histology 22-23.

CLINICAL FEATURES

Patients with MPBC usually present with hematuria,
dysuria, urgency, frequency, urinary obstruction, urinary
infection, weight loss and, as for upper tract tumors,
flank pain 1-4. Most MPBCs are diagnosed at an
advanced stage with muscle-invasive or metastatic dis-
ease 1,3-5. Even when they represent only a small frac-
tion of the overall tumor volume 3,12,25-24 this feature con-
fers a poor prognosis. Such aggressive behavior has
been attributed to a high level of inherent chromosomal
or genomic instability, with higher DNA contents than
conventional UC 1,35. Another putative explanation is
the increased expression of molecular markers that are
conventionally associated with poor prognosis, such as
p53, MIB-1, Aurora-A, and surviving 36-40. It would be
interesting to test in this setting novel molecular markers
currently under evaluation in the setting of prostate
cancer 41-43.

The dismal prognosis of MPBC has been questioned
by other studies comparing the clinical course of MPBC
and conventional UC after cystectomy 44-45. In a huge
case series of more than 800 MPBCs, the median
overall survival of these patients was nearly half that of
conventional UC (44.7 vs 91.9 months; p < 0.001) 9.
However, when stage matched the one of patients with
pure UC, MPBC had similar rates of local/distant recur-
cence and cancer specific survival 46.

Vourganti et al. compared MPBC to conventional UC in
a Surveillance, Epidemiology and End Results (SEER)
based outcome study and found that stage for stage,
MPBC had a similar survival profile to conventional UC
except for non-muscle invasive disease which was as-
associated with worse survival 47.

On the other hand, markers of an adverse clinical course
such as occult nodal metastases and lymphovascular
invasion are often reported in case series of MPBC, the
latter typically found peripheral to the primary tumor
mass 1.5. In such cases, 5- and 10-year survival rates
may be as low as 25 and 24%, respectively 5,21,48.

The aggressive nature of this variant is supported by
the occurrence of MP morphology in metastatic lesions
and by the worse biological behavior of combined
MPBC and conventional UC, supporting the aggressive
nature of this variant 1,8,25,35. In the latter case, mixed
neoplasms with > 50% MPBC carry a relative mortal-
ity risk of 2.4 as compared with pure conventional UC
or < 50% MPBC 12. It is therefore recommended to
report the presence and the proportion (in percentage)
of MP component in the pathology report of a UC 35-49.

In a single study, a 10% cut-off of MPBC was reported
to have a clinically significant effect on disease specific
survival 25; this has turned into reporting of even focal
amounts of MPBC. However, many conflicting reports
exist ranging from those stating that the mere presence
of MPBC is clinically relevant 8 to others stating that
focal MPBC portends better outcomes than extensive
disease 10,50.
TREATMENT

The standard treatment for conventional urothelial MIBC is radical cystectomy (RC), possibly with neoadjuvant chemotherapy. Due to its poor prognosis, micropapillary MIBC is considered a strong indication to perform RC as a first-line therapy instead of neoadjuvant chemotherapy. The poor prognosis of MPBC and disparities in treatment response may be explained by underlying differences in tumor biology between UC and MPBC. The available literature is limited to retrospective subgroup analyses of some randomized trials, thus leading to conflicting results. Some studies, including a phase III trial reported a better response to neoadjuvant chemotherapy in tumors with mixed histology and/or pure MPBCs than in pure UC (four cycles of gemcitabine and cisplatin in most cases), while other studies failed to demonstrate any significant difference in outcomes with the addition of neoadjuvant chemotherapy in patients with muscle-invasive MPBC undergoing RC. On the other hand, a recent study of predictors of pT0 after neoadjuvant chemotherapy found that variant UC histology predicted against pT0 compared to pure UC (OR 0.09, 95% CI 0.021-0.380). A study of 82 patients treated at Memorial-Sloan Kettering found that neoadjuvant chemotherapy may be useful in muscle-invasive MPBC. In their cohort, the 29 patients who received neoadjuvant chemotherapy (mostly gemcitabine-cisplatin) were more likely to have no evidence of residual disease at the time of RC when compared to immediate RC (pT0 rates of 45 vs 13%, respectively; p = 0.049), which is similar (38 and 15% respectively) to the pT0 rate seen in the neoadjuvant SWOG trial. The study by Meeks et al. failed to show any difference in survival between neoadjuvant chemotherapy and immediate RC but there was a significant improvement in overall survival for patients who achieved pT0 (2-yr CSS of 78 and 25% respectively, p = 0.05), though the follow-up was relatively short. Recently, Fernandez et al. reported that neoadjuvant chemotherapy appears to confer benefit to patients with MPBC without tumor-associated hydrenephrosis, while patients with cT1 disease may undergo standard surgical treatment.

The standard treatment for conventional urothelial NMIBC classified as high-risk is intravesical instillation of Bacillus Calmette-Guerin. The presence of micropapillary morphology seems in NMIBC has been reported to severely impair the efficacy of intravesical BCG treatment, although different studies yielded conflicting results. Kamat et al. examined a series of 44 patients with non-muscle invasive MPBC, finding a non-significant trend towards improved survival in the immediate cystectomy group. An update of the MD Anderson MPBC series in 2014 focused on 72 cases of cT1N0M0. Upfront RC was utilized in 36 (n = 26) while 55% (n = 40) received primary BCG. In the primary BCG cohort, 45% progressed to muscle-invasive disease and 35% developed lymph node metastasis. At 5 years, disease specific survival was 62% for the delayed RC group compared with 100% for the upfront RC group (log rank p = 0.015). However, the Memorial Sloan Kettering Cancer Center reported on their experience with 36 patients with non-muscle invasive MPBC in 2014. Early RC was utilized in 15 and conservative therapy in 21. They found that five-year disease specific mortality (17% vs 25% respectively; p = 0.08) and the five-year incidence of metastasis (21 and 34% respectively; p = 0.09) were not significantly different between the groups. Other smaller retrospective series that contain patients with non-muscle invasive MPBC have been reported. Ghoneim et al. reported on 10 patients diagnosed with cTis-cT1 disease, of whom 7 received intravesical BCG and 3 underwent upfront RC. All 7 patients treated with BCG recurred (4 progressed) and underwent delayed RC with resultant pT3 disease. Furthermore, positive lymph nodes were detected in 6 patients. Comperat et al. reported on a 72 patients’ cohort of MPBC including 12 cTa MPBC cases, of which 8 were treated with RC. All 8 were found to have invasive carcinoma at the time of surgery including 5 (63%) with pT2-pT4 disease. A recent 120 patient SEER 17-based study also showed that non-muscle invasive MPBC was associated with worse overall and disease specific survival outcomes in a population based study when compared to conventional UC. These studies all suggest that non-muscle invasive MPBC is associated with more aggressive disease and worse survival than would be expected for conventional NMIBC and may warrant more aggressive intervention.

Another study argues that non-muscle invasive MBPC may have a different histologic presentation than muscle-invasive MPBC as the authors suggest the former to be more “urothelial” in appearance than the often “glandular” muscle invasive MPBC. Of the 18 patients in this report, treatment data was available on 13; 7 (54%) underwent primary intravesical therapy, 5 (38%) underwent initial surveillance only, and 1 (8%) underwent RC. Three patients progressed to muscle invasion (pT2, pT3, pT3N2). One patient died of bladder cancer, one died of other causes, and 64% are alive with an intact bladder after a median follow up of 14 months. In a report by Gaya et al. on 8 patients with non-muscle invasive MPBC, 6 (75%) patients (small proportion of MPBC relative to conventional UC) were reported to be disease free after BCG therapy with a 5-year DSS of 87.5%. Despite the limited sample size, this report suggests that BCG may be appropriate for non-muscle invasive MPBC.
Overall, data suggest that the biology of non-muscle invasive MPBC is different from that of conventional UC and it's associated with an aggressive phenotype with high failure rates of intravesical therapy. This viewpoint is consistent with the opinion of the respondents to a survey developed in 2010 by the Translational Science Working Group of the Bladder Cancer Advocacy Network sponsored Think Tank meeting and distributed to members of the Society of Urological Oncology, with 80.5% advocating for early cystectomy (7.6% with neoadjuvant chemotherapy) for cT1 MPBC; this was one of the few therapeutic approaches with relative consensus.

Obviously, factors predicting disease outcome would be extremely welcome, ranging from simple clinical features, like smoking habits, to molecular markers representing different pathways potentially involved in tumor response to available treatments. Recent evidence suggests that such markers, apart from having predictive value, may represent novel potential therapeutic targets.

To conclude, MPBC is a rare variant of BC that usually affects the elderly. Correct pathology identification of this variant histology, including its stage and its percentage within the tumor, has prognostic value and therefore is essential to plan treatment. Non muscle invasive MPBC seems to have worse behavior than non muscle invasive conventional UC, thus requiring early aggressive treatment. In muscle invasive cases, the role of neoadjuvant chemotherapy before radical cystectomy is controversial. Like for other common urological conditions, case volume and treatment tailoring to patient and local clinical conditions remain a key issue. Insights into its peculiar behavior are crucial for a proper management.

Acknowledgements

We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

Conflict of interest

The authors declare no conflict of interest.

References

Amplification/overexpression of a mitotic kinase gene in human bladder cancer. 

**Pathological characteristics of microcapsular transitional cell carcinoma:** a highly aggressive variant. J Urol 2000;163:748-51.

**Microcapsular variant of urothelial carcinoma of the urinary bladder:** a clinicopathological and immunohistochemical study. Histopathology 2004;45:55-64.

**Immunohistochemical panel to identify the primary site of invasive microcapsular carcinoma.** Am J Surg Pathol 2009;33:1037-41.


**Expression profile of the clinically aggressive microcapsular variant of bladder cancer.** Eur Urol 2016;70:611-20.

**MiR-29b and miR-29c expression is predictive of response to BCG treatment in T1G3 bladder cancer.** Anticancer Res 2009;29:4201-4.


**Clinical features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis.** BJU Int 2013;111:325-30.

**Impact of neoadjuvant chemotherapy and cystectomy on outcomes of cT1 micropapillary bladder cancer.** J Urol 2015;193:1129-34.

**Clinical outcomes of cT1 microcapsular bladder cancer.** J Urol 2015;193:1129-34.


Role of age in prostate and bladder cancer. A critical overview

F. Sanguedolce1, M. Chirico2, G. Stallone3, L. Cindolo4, A. Tewari5, G. Carrieri2

1 Section of Pathology, Department of Clinical and Experimental Medicine, University of Foggia, Italy; 2 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 3 Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 4 Department of Urology, ASL02 Abruzzo, ‘S. Pio da Pietrelcina’ Hospital, Vasto, Italy; 5 Department of Urology, Mount Sinai School of Medicine, New York, USA

INTRODUCTION

According to the latest worldwide cancer statistics, prostate cancer (PCa) ranks first cancer in males and bladder cancer (BC) ranks seventh cancer in both genders. Their incidence increases with age, reaching age-standardized incidence rates of 283.3 and 51.1, respectively. Therefore, these tumors stand out as major health problems and, in the elderly, they pose additional issues related to patients’ comorbidities as well as treatment efficacy and adverse reactions. Herein, we attempted to provide a comprehensive overview regarding diagnostic and treatment issues in elderly patients with PCa or BC with special attention to the role of age in such patients.

PROSTATE CANCER

In male patients, the incidence of PCa diagnosis increases steadily with age. The GLOBOCAN 2018 worldwide estimated age-standardized incidence rates range from 10.2 (age group < 65y) to a stunning 283.3 (age group ≥ 65y)1.

Age has been suggested to be a relevant prognostic factor in several diseases. According to the latest statistics, prostate and bladder cancer are among the most frequent urogenital tumors and their incidence increases with age. Available data suggest that age may drive the diagnostic and therapeutic pathways of both prostate and bladder cancer. Contrary to common perception, age seems to have a negative prognostic impact on many aspects of such cancers. Age per se does not seem to represent a contraindication to actively search for and treat such cancers but it would rather be a factor to be taken in due account in the decision-making process.

Key words: Bladder cancer, Prostate cancer, Ageing, Diagnostic issues, Treatment options
Another issue to be taken into account in the diagnostic pathway is the frequent association of aging with benign prostatic hyperplasia (BPH) as well. Indeed, BPH is a chronic disease whose incidence increases with age, reaching 80% in males aging 70 to 80 years.

Elderly males tend to seek medical advice due to symptoms related to BPH and benign prostatic obstruction (BPO); such symptoms have been shown to play a role in the differential diagnosis between these two common urological conditions of the elderly male.

However, patients may suffer both conditions but its frequency is not definitely known.

Emerging novel tools in the differential diagnosis between BPH/BPO and PCa include novel biomarkers such as a Pentraxin 3 and EGR2 and multiparametric magnetic resonance imaging (mpMRI). Their role is currently under definition. In the meanwhile, optimizing prostate biopsy protocol and pathology report play a key role in obtaining diagnosis and defining patient’s risk.

**Treatment options**

The extent of expected survival is a key factor in choosing the proper treatment strategy in PCa patients. Recent reports suggest that in current clinical practice old men with PCa receive insufficient diagnostic workup and subsequent curative treatment; accordingly, US data provide evidence that old age (> 75 years) is an independent predictor of receiving external beam radiation therapy instead of radical prostatectomy in men with localized PCa. This may be partially due to the putative occurrence of adverse post-surgical side effects in the elderly, although our data failed to find a significant association between age and anastomotic urinary leakage following retropubic radical prostatectomy. External beam radiotherapy seems to provide similar cancer control regardless of age but reported 5-y biochemical recurrence-free survival in high-risk PCa remains relatively low and patients should be warned about possible urinary and gastro-intestinal side effects.

Androgen deprivation therapy (ADT) is not indicated for elderly patients in good general condition with locally confined prostate cancer. Conversely, PSA recurrences after radical prostatectomy should be treated primarily with hormonal therapy. In case of asymptomatic metastases, ADT is associated with a lower progression rate than initiating treatment only when symptoms arise. However, ADT is associated with several adverse reactions such as depression, cognitive impairment, osteoporosis and cardiovascular complications, that should be taken in to account, particularly in elderly patients. This scenario sets a potential role for novel minimally invasive procedure such as cryotherapy, whose role in the elderly deserves to be investigated.

**Outcome issues**

Age-standardized mortality rates rise almost tenfold with advancing age at diagnosis, ranging from 16.0 in the 55-69 age group to 142.8 in the > 70 age group. Some evidence however exists that in case of localized PCa mortality is decreasing with age, due to high incidence of life-threatening diseases in the elderly. Moreover, a meta-analysis of articles addressing the role of age in localized PCa from 1966 to 2000 outlined that age has no significant prognostic effect in contemporary series. Obviously, these estimates may be biased by the vast treatment (mostly surgery alone and radiotherapy alone) and population’s heterogeneity. However, similar results have been achieved by a most recent report of more than 2000 patients treated by radical retropubic prostatectomy for PCa staged up to pT3b. The authors assessed the prognostic role of age without the effect of the primary confounding variables (serum PSA level, Gleason score, percentage of positive biopsy cores) by a direct-paired analysis, and found that age was not an independent prognostic factor. One study, whose clinical endpoint was biochemical recurrence, yielded similar results, while another one yielded different results.

In spite of such controversies, age is incorporated in risk classification systems, such as the age-adjusted Charlson Comorbidity Index, to predict disease outcome after radical prostatectomy.

Aging has also been proved to be related to clinical and pathological parameters both directly and indirectly associated to outcome, such as advanced disease, post-operative upgrading, high Gleason score and grade group, and occurrence of bone metastasis.

**Bladder cancer**

Bladder cancer (BC) is traditionally regarded as a disease of the elderly. Its overall incidence increases abruptly from a very low age-standardized rate of 2.3 in patients < 65y to a 51.1 rate in patients ≥ 65y; its mortality rates range from 0.5 to 20.4 in the same age groups, and such data apply to both genders. The most common risk factors for BC are smoking, male gender, exposure to environmental or occupational carcinogens and the age.

From a clinical standpoint, two types of BC exist, namely non-muscle invasive bladder cancer (NMIBC) that account for approximately 75% of all tumors and muscle invasive bladder cancer (MIBC). Such proportion remains constant throughout ages.

**Diagnostic issues**

Transurethral resection of the bladder tumor (TURBT) remains the first and mainstay method of local tumor
staging. Not to mention that in elderly people with other malignancies TURBT is essential to rule out other primaries. In other words, the onset of hematuria and/or a bladder mass in an elderly patient should not prompt a diagnosis of bladder primary without a TURBT, as secondary lesions from more frequent tumors such as colon, breast, or lung cancer may occur in this age group.

Patients diagnosed with NMIBC are stratified in risk categories based on several clinico-pathological parameters (EORTC) and such stratification is used to plan treatment. Age belongs to prognostic parameters as it has been shown to represent the most important prognostic factor for overall survival along with tumor's grade.

EAU guidelines however recognize that available clinico-pathological prognostic factors are not that efficient in assessing tumor biology and consequent behavior. In order to choose the proper treatment for NMIBC patients, especially those ones with high-risk tumors, several attempts have been made to achieve an optimal stratification by assaying different molecular markers. Since intravesical instillation of Bacillus Calmette-Guerin (BCG) is the standard treatment for high-risk NMIBC, attempts have been made to identify molecular markers, such as Retinoblastoma protein (pRb), Human epidermal growth factor receptor 2 (Her-2), p53, p21, or survivin, which could reliably predict response to such treatment and consequent disease outcome. Moreover, there is emerging evidence that the combination of markers is more effective than the single ones in predicting treatment response and disease outcome. Further focused studies on a validated combination of clinic-pathological and molecular markers are necessary.

Treatment options
The standard of care in high-risk NMIBC remains intravesical instillation of BCG. However, being based onto efficiency of the immune system, the efficacy of such treatment in elderly has been questioned. Moreover, a greater risk of adverse events has been postulated, such as fever, hematuria, urinary symptoms and clot retention or more severe related to intravascular dissemination of tubercle bacillus. This issue deserves attention in order to avoid patients not receiving effective treatment for their high-risk NMIBC only on the basis of anagraphic age.

As for MIBC, radical cystectomy (RC) stands out as the treatment of choice in most cases. RC seems, however, to carry a complication rate as high as 40-60% in the elderly; on the other hand, evidence exists that RC is associated with the greatest risk reduction in disease-related and non-disease-related death in patients > 80y. Having said this, biological age (i.e. presence of comorbidities) is far more important than chronological age as a prognostic factor for MIBC patients undergoing RC. As always, a careful patient’s evaluation should be carried out in planning treatment for MIBC and validated tool, such as the Charlson Comorbidity Index (CCI) may be useful in the decision-making process. On the other hand, like for other common urological conditions, treatment should be tailored to local conditions and wise intraoperative clinical judgment. RC is more and more accepted also in octogenarians but the use of continent urinary diversion in such age population remains controversial. Moreover, case volume seems to impact on outcomes, as in other surgical fields. Robotic RC offers the advantage of reduced invasivity, but this is counter balanced by length of the procedure and pneumonia. Moreover, potential complications associated to specific procedural steps should be taken into account.

Finally, questions remain regarding feasibility, efficacy and safety of adjuvant systemic chemotherapy in the elderly patient with MIBC, as the potential benefit should be carefully weight against the almost inevitable toxicity of such treatment. Like in other urological cancers, immunotherapy is recently emerging as a promising option in patients with advanced disease. Specifically, checkpoint inhibitors (PDL-1 and PD1) yield great promise in patients failing or unsuitable for chemotherapy. Whether or not immunosenescence may impair response to such treatment deserve further investigation.

Acknowledgements
We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

Conflict of Interest
The authors declare no conflict of interest.

References
Role of age in prostate and bladder cancer. A critical overview.


Nephrolithiasis in the elderly

A. Carella¹, S. Leo¹, B. Infante¹, A. Hoznek², G. Grandaliano¹, G. Stallone¹

¹ Nephrology Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Department of Urology, Henri Mondor Hospital, Créteil, France

Introduction

Nephrolithiasis is a disease characterized by the presence of crystal concretions in the urinary tract. It is widely spread worldwide, both in the Western and non-Western countries. Several studies have pointed out a rising prevalence and incidence of kidney stone disease in the elderly population in the last several decades. Data from large cohort studies suggest an association between the increased risk of stones formation and dietary factors such as low fluid intake, low calcium intake, high sodium intake, high animal protein intake, and high fructose intake. The kidney stones risk may also be increased by medical conditions such as obesity, diabetes, primary hyperparathyroidism, and gout. Stones may be asymptomatic or may show symptoms such as abdominal and flank pain, nausea and vomiting, urinary tract obstruction, and infections.

This review aims to outline specific features of nephrolithiasis in the elderly population, including lifestyle, eating habits, hormonal modifications and comorbidities that may affect stone formation. We also assessed the impact of age on diagnostic and therapeutic pathways. Evidence suggest that age per se should not preclude standard treatment but should be taken in due account during the decision-making process.

Key words: Nephrolithiasis, Elderly patients, Epidemiology, Risk factors, Treatment

Introduction

Nephrolithiasis remains one of the most challenging diseases for clinicians worldwide because of the high prevalence of subjects experiencing kidney stone formation (13 for men and 7% for women) and the elevated rate of reoccurrence after the first episode (approximately 50% within 5 years)¹. It is common during adulthood with a higher prevalence between 40-50 years, but its incidence is increasing in patients older than 65 year old². This is partly due to increase in life expectancy over the last decades, mainly in Western countries.

Indeed, the general demographic statistics underline that the population aged 65 years or more will rise to the 28% of the general population in 2050 (about 2 billion people), thus further increasing the prevalence of nephrolithiasis in geriatric patients³ to 19.1% in men and 9.4% in women. It is estimated that the elderly will represent 10-12% of all stone formers⁴. Elderly patients deserve specific attention in consideration of their frequent comorbidities, different dietary habits, with low fluid intake and decreased high-nutrients food consumption, physical and environmental factors and hormonal changes⁵.

Accordingly, the management of elderly patients requires an accurate diagnostic evaluation and tailored treatment, both pharmacological and surgical, to obtain results similar to their younger counterpart. McCarthy et al. compared patients aged 80 year-old or more with a younger cohort highlighting that, although elderly had more comorbidities, later presentation with larger and more complex stones, required early ureteric stent insertion and definitive percutaneous nephrolithotomy (PCNL), there was no difference in intraoperative
complications and as much as 39% of them could be managed on outpatient basis. Thus, we need to appreciate the relevance of urinary stones disease in the elderly and its association with systemic diseases like obesity, diabetes and cardiovascular disease.

**EPIDEMIOLOGY**

Kidney stones are a common disease in industrialized nations, with an incidence of 1/1000 persons and a risk of 13% in men and 5% in women. In these countries, the prevalence of renal stones has increased to 8.8% in the 2000s, in association with the rising incidence of insulin resistance, type 2 diabetes mellitus, obesity, and cardiovascular disease. These are the consequences of sedentary lifestyle and high-protein diets leading to a higher urinary excretion of lithogenic factors (calcium, phosphates and uric acid) and to an increased urinary acidity.

In the general population it is possible to recognize different kinds of stones, depending on their chemical composition: calcium oxalate, calcium phosphate, uric acid, magnesium ammonium phosphate (struvite) and cystine. Each type presents a different prevalence, with the majority of stones formed by calcium oxalate (26.3%), followed by calcium phosphate and uric acid stones (7.4 and 4.5% respectively). Stoller et al. suggested higher incidence of uric acid stones in older patients, whereas other studies report the most common stone type in patients over 65 years being calcium oxalate. Furthermore, stone composition changes worldwide: in the Mediterranean area, stones are more likely to be composed by uric acid (75%), whereas in USA, calcium phosphate and calcium oxalate stones are the most widespread (70%). Even the stone forming trend varies with geographic distribution, growing from North to South, due to higher temperatures and sunlight exposure that increase vitamin D production, with subsequent greater hypercalcemia, as well as insensible losses of water, leading to higher urine concentration. An higher urinary calcium concentration in a smaller urinary volume promotes the downfall of crystals, leading to stone formation.

Regarding older population and its typical comorbidities, Alexander et al. have highlighted the association between nephrolithiasis and systemic disease, such as chronic kidney disease, metabolic syndrome, cardiovascular disease and osteoporosis. Furthermore, they have observed a major risk of end stage renal disease (ESRD) when one or more kidney stone episode occurred. Ferraro et al. pointed out a relevant relationship between heart disease and stone formation, as they found, in a prospective study, that patients with a history of kidney stones presented a statistically significant increased risk of coronary artery disease.

**RISK FACTORS**

Risk factors for stone formation can be classified in organic (i.e. malformations of the urinary tract) and functional (metabolic imbalance). Specifically, for patients aged 65 years and older, conditions correlated with stone formation include: reduced mobility, low fluid intake, chronic infections, menopause for women as declined endogenous estrogen levels and enhances the risk of recurrent urinary tract infections, increase of fat mass and bone mass reduction. In addition, it has been discussed whether a major calcium dietary intake and pharmacological calcium supply, often prescribed in elderly in the attempt to prevent osteoporosis, may increase stones formation, because of the higher urinary calcium levels. Indeed, Jackson et al studied a cohort of 36282 women in post-menopausal state, between 50 to 79 years, that were given 400 IU of Vitamin D and 1000 mg of oral calcium per day and found a 17% higher rate of kidney stones. Obesity, a disease often seen in elderly, is another important factor associated with nephrolithiasis. As suggested by Willet et al., BMI is tightly correlated with stone formation, with an association stronger for women than for men. Other authors have further characterized BMI influence on the risk of kidney stone formation. In particular, for women, the relative risk with a BMI higher than 35 kg/m² was greater than with a BMI of 30 kg/m². It is possible that an increased BMI is related to a major excretion of promoters and and a reduced urine concentration of inhibiting factors of stone formation. Ekeruo et al. observed an important association between lithogenic factors (calcium, phosphate, oxalate and uric acid excretion as well as higher urinary pH) and BMI. On the other hand, they also report increased urine levels of some protective factors citrate in subjects with high BMI. Finally, obesity may lead to insulin-resistance that modifies urinary pH and uric acid levels, causing formation of uric acid stones. In addition, obese patients with insulin-resistance are exposed to a greater risk of gout, a further promoter of uric acid stone formation.

**PATHOGENESIS**

The pathophysiology of stone formation is multifactorial because several physical and chemical factors may contribute.
Urine is characterized by the presence of different molecules in a status of mutual equilibrium preserved by urinary pH, urinary saturation level and calcification inhibitors. Whenever one of these factors is modified, thus altering such “equilibrium stability state”, urine becomes supersaturated of ions that may combine to create stones. Indeed, these ions, when reaching the condition of supersaturation, might pass from a solution phase to a solid crystal phase. Interestingly, supersaturation is not affected by ions concentration, but by free ions activity, which depends on urinary pH, crystal component concentration and inhibitors of stone formation.

When ions activity enhances and the crystal component concentration increases, calcification inhibitors can reduce stone formation binding the ionic constituents of the stone in soluble complexes. Thus, the presence of inhibitors in urine increases the level of supersaturation required to form the calculi solid phase and delays the expansion of the crystals already shaped. When a specific ion activity prevails in the solution, ions join together in a stable solid phase, in the nucleation process, which might be a homogeneous nucleation or, more commonly, a heterogeneous nucleation. In the former, the nucleus of the stones is composed by the same ion crystals whereas in the heterogeneous process, the nucleus is represented by other substances, including cell debris or a mucoprotein matrix. For example, calcium oxalate crystals and uric acid crystals may aggregate into bigger stones, transfer to the urine, producing crystalluria.

The second phase in stone formation is the enhancing process, also divided into homogeneous or heterogeneous. The basis of this mechanism may be both organic or functional. For example, 10% or more of kidney stones is associated with malformative diseases of the urinary tract such as medullary sponge kidney (or Cacchi-Ricci disease) and Autosomal dominant polycystic kidney disease. Functional factors play a key role in the pathogenesis of kidney stones and can be represented by endocrine changes such as primary hyperparathyroidism, metabolic alterations such as hypercalciuria, hyperoxaluria, or other disregulations of the uric acid, cystine and xanthine metabolisms. Hyperparathyroidism or other bone disorders, including osteoporosis and reduced mobility, peculiar of the elderly, characterized by a greater mobilization of bone calcium might cause a reabsorption hypercalciuria. The hypercalciuria may be also due to an increased enteric reabsorption or to a deficit of the kidney tubule that does not adsorb filtrated calcium. This last condition induces low blood calcium levels and secondary hyperparathyroidism that, in turn, will maintain the hypercalciuria.

The pathogenic pathway leading to other types of stones is represented by metabolic alterations. For example, uric acid is the final product of endogenous and exogenous purine metabolism through the oxidation catalyzed by xanthine oxygenase, circulates in blood as urate and it is mainly disposed by kidneys. Considering that the solubility of uric acid is low, when its serum levels rise and urinary pH reduces, crystals of uric acid formation occurs, as it is possible to observe in lymphoproliferative disease and in the gout.

**CLINICAL MANIFESTATIONS**

The clinical features of kidney stones are aspecific symptoms which are due to their location in the kidney, ureter or urinary bladder: pain, hematuria, urinary tract infections (UTIs) and, even, acute kidney injury (AKI), when kidney calculi cause bilateral renal obstruction or unilateral obstruction in a single functioning kidney. The pain, known as ureteral or renal colic, arises abruptly, might be severe and appears when the stones partially or totally occlude the urinary tract. Usually, the pain is localized in the kidney area, migrates anteriorly to the abdomen wall and may be subsequently referred to the external genitals. This change occurs when stone gets through ureterovesical junction. In this phase, microscopic or macroscopic hematuria is constantly present. In addition, patients with kidney stone disease may frequently experience recurrent UTIs, because the stone represents a “sancta sanctorum” where bacteria cannot be reached by antibiotics. Sometime, on the other hand, infections, modifying physico-chemical urinary composition through urease producing bacteria, might induce stone formation.

Bauza et al. demonstrated the presence of bacterial growth in cultures of stones removed by endourological procedures. In these circumstances, it is possible to notice UTIs symptoms, as well as stranguria, pollakiuria, urinary urgency, even fever. In the worst cases, acute kidney injury (AKI) complicates the clinical picture. AKI is observed in 15% of hospitalized adult patients with kidney stones.

AKI in this setting is significantly more frequent in the elderly population in consideration of a “physiological” in the renal functional reserve. Aging, indeed, produces a decline in renal mass, progressive glomerular atrophy, glomerulosclerosis, tubulointerstitial fibrosis. These pathological changes underlie the progressive fall in glomerular filtration rate (GFR) starts and renal plasma flow (RPF) observed in this patients population, facilitating kidney injury in case of obstruction.
**DIAGNOSIS**

Nephrolithiasis clinical evaluation comprises multiple steps. It is useful to examine stone history, such as number of stone formed, frequency, stone type, association with UTIs, kidney involved (unilateral or bilateral). General medical history is important, because several drugs predispose to calcium stone or potentiate uric acid stone formation. Furthermore, it is essential to evaluate fluid intake and dietary style that change in older patients. In fact, elderly patients are affected by a natural decrease in fluid intake that results in exceedingly concentrated urine that, in turn, facilitates stone formation and enlargement. Usually dietary intake in geriatric population is low in many nutrients, particularly calcium, leading to not only bone demineralization, but also to an increase in stone formation. Obviously, laboratory findings play a key role in the correct management of stone disease. It is essential to drive a complete metabolic analysis, including urinalysis, urine culture, stone analysis and blood chemistry (calcium, sodium, bicarbonate, phosphorus, uric acid, parathyroid hormone level).

Once clinical examination has been completed, imaging techniques play a key role confirming or not kidney stones diagnosis and identifying stones site, size and number. The most suitable imaging evaluation for kidney stones depends on clinical situation and the stone type. Imaging techniques able to diagnose kidney stones include ultrasound (US), abdominal radiography, intravenous pyelography (IVP), non-contrast-enhanced computed tomography (CT), US represents the primary diagnostic choice, being safe for risk of radiation and reproducible. US sensitivity and specificity are high, with 90 and 65-84% rate respectively, whereas the specificity is decreased by the frequent false positive caused by the morphological variability of the urinary tract. However, US finding tightly relies on stone size (it is possible to identify calculi larger than 5 mm in the 91% of cases) and localization (63% for ureter, 90% for urinary bladder and 85-88% for other sites).

However, in case of acute urolithiasis, non-contrast-CT has become the gold standard, being able to determine stone diameter, density, inner structure, skin-to-stone distance. Indeed, non-contrast-CT is rated as a more accurate imaging technique than US in the nephrolithiasis diagnosis process, because CT improves stone size and site determination and highlights nephrological and urological complications. Consequently, non contrast-CT is currently acknowledged as the most reliable imaging technique in nephrolithiasis diagnosis, reaching a sensitivity of 94-100% and a specificity of 94-97%.

**TREATMENT**

Once the diagnosis has been reached, the management of these patients depends on several factors that should be carefully evaluated, particularly in the elderly. The medical treatment for renal colic, an intense cramping pain, should be non steroid anti-inflammatory drugs, paracetamol or morphine-like drugs.

Concomitant UTIs requires antibiotic therapy, possibly sensitivity-guided, whereas fever not subsiding by early antipyretics and antibiotics often requires immediate drainage of the collecting system by ureteral stenting or nephrostomy. In such cases, active stone treatment by extracorporeal shock wave lithotripsy (ESWL) and ureteroscopic or percutaneous removal should be delayed to resolution of the infection.

Ureteral stones may be suitable for observation, in the absence of infection and after the acute phase. As much as 90% of ureteral stones up to 4 mm may pass spontaneously. Medical treatment to facilitate expulsion may be used as well, though efficacy of the current drug of choice (tamsulosin) is often questioned. Renal stones may also be suitable for observation, providing they remain asymptomatic, cause no UTI, and do not grow rapidly. This clinical condition, i.e. the asymptomatic renal stone, can often represent a diagnostic dilemma, particularly in the elderly. While observation would appear particularly suitable for the elderly, one should bear in mind that such patients may have reduced efficiency of their immune system potentially leading to serious infectious complications.

When planning active stone treatment by ESWL, ureteroscopic or percutaneous procedures, several factors should be taken into account ranging from patient general status and wish, stone size, position, presumptive composition, anatomy of the urinary tract, concomitant bacteriuria etc. Given the risk of potentially lethal septic complications associated with endourological procedure, great attention has been paid to develop guidelines for proper antibiotic prophylaxis and management of infective complications. Question remains whether such procedures are associated with greater risks in the elderly population. Some reports pointed out no significant difference in the outcome of flexible ureteroscopy and retrograde intrarenal surgery in the elderly, though case volume may play a relevant in this setting.

The issue of percutaneous nephrolithotripsy (PCNL) seems to be more complex, because it has been seen as a challenging procedure in this patient population. Specific procedural issues that may impact on outcomes, particularly in the elderly, range from patient positioning to the procedure exit strategy.
FINAL REMARKS

Elderly patients have become a wide part of the entire kidney stone population. As a consequence, kidney stone disease is a clear medical concern for people aged 65 years or more, given their frequent comorbidities such as insulin resistance, type 2 diabetes mellitus, obesity, and cardiovascular disease. While the entire decision-making process should take in due account not only such known comorbidities but also the potentially occult ones, particularly immunosenescence, age per se should not preclude effective treatments.

CONFICT OF INTEREST

The authors declare no conflict of interest.

References

A. Carella et al.


Molecular markers predicting disease outcome in bladder cancer. Should we shift from the classical cell-cycle regulators to HER2 oncogene?

F. Sanguedolce, A. Cormio, B. Calò, N. Buffi, R. Autorino, L. Cormio

1 Section of Pathology, Department of Clinical and Experimental Medicine, University of Foggia, Italy; 2 Department of Biosciences, Biotechnologies and Biopharmaceutics, University of Bari, Italy; 3 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 4 Urology, Humanitas Clinical and Research Hospital, Rozzano, Milan, Italy; Humanitas University, Rozzano, Milan, Italy; 5 Division of Urology, Department of Surgery, VCU Health, Richmond, VA, USA

INTRODUCTION

Bladder cancer is regarded as a disease of the elderly as its incidence increases steeply with increase in age. One of the main clinical issues in bladder cancer is predicting disease outcome. Since the unpredictable behavior of this disease has been attributed to its biology, the search for predictive factors has mainly been oriented towards molecular markers. Cell-cycle regulators are the most studied ones but there is emerging evidence that HER2 oncogene, widely studied and used in other cancers, may soon overcome them. Herein we reviewed available evidence regarding the predictive role of cell-cycle regulators and HER2 oncogene. Emerging data suggest that HER2, either alone or in combination with other markers, can be equally if not more effective than cell-cycle regulators in predicting disease outcome. Moreover, it represents a well-known and particularly attractive potential therapeutic target.

Key words: Molecular marker, HER2, Bladder cancer, Oncogene

INTRODUCTION

Bladder cancer is the sixth most common malignancy worldwide in males, with estimated age-standardized incidence and mortality rates in 2018 of 9.6 and 3.2, respectively, increasing to 89.5 and 35.4 in the elderly group (65+) [1]. In this age group, BC is the eighth most frequent cause of cancer-related deaths accounting for over 110,000 deaths each year [1]. According to several studies, BC has been shown to be a heterogeneous disease on a clinical, histopathological, and molecular grounds. First of all, the presence/absence of tumor cells in the muscularis propria distinguishes two main clinical types of BC, the non-muscle invasive (NMIBC) and the muscle invasive (MIBC) forms, carrying different genetic profiles, clinical behavior, and prognosis. Nevertheless, the ongoing management of both NMIBCs and MIBCs is largely based on conventional parameters, mostly stage and grade [2,3], though other simple clinical factors like smoking seem to play a role [4]. Molecular subtyping has become a routine tool in the management of several types of malignancies, such as breast cancer, since pathogenesis and progression are based on well-known changes in different molecular pathways. Mutations on a genetic and/or epigenetic level result in severe impairment and loss of cell homeostasis and function. Moreover, the type and amount of molecular alterations are a predictor of tumor aggressiveness; therefore, they are suitable markers for patients’ risk stratification as well as putative therapeutic targets.
In BC, a large body of literature exists about such tumor-related molecular markers but their use in clinical practice has a long way to go: main reasons are the high heterogeneity of study designs, the lack of rigorous validation processes, and the unfavorable cost-effectiveness ratio as compared to conventional clinicopathological parameters.

Aim of this review is to assess the current knowledge in the use of the most promising biomarkers with prognostic/predictive value and therapeutic potential in BC.

CELL-CYCLE REGULATORS

Most, if not all, human cancers rely on mutations of cell-cycle regulatory genes, which are involved in the progress of the cell through the various phases of its life, including growth, DNA synthesis, replication, by activation of specific checkpoints. In BC, the most studied cell-cycle molecules are P53 and PRB, both coded by tumor suppressor genes. P53 may act as a sequence-specific transcription factor under genotoxic conditions; allelic loss or point mutations result in a prolonged half-life and nuclear accumulation of the protein, which can therefore be detected by immunohistochemistry on paraffin-embedded BC tissues, as highlighted in a large meta-analysis by Malats et al. 5. P53 status has been regarded as a prognosticator of progression, disease-free and disease-specific survival (DFS and DSS) in both NMIBC and MIBC in several studies, yet with conflicting results 6-9. In NMIBC, P53 overexpression has been reported to be significantly related to higher progression rates and lower cancer related survival 10 11, while in MIBC its prognostic role seems to decrease with increasing tumor stage 12 13. As a predictive marker to BCG response in high-grade T1 BC, P53 status has not shown convincing results so far 14-19, probably due to statistical errors associated with the small numbers of patients tested and inter-observer variation in assessing P53 staining. According to some authors, P53 expression may severely impair the response to DNA-damaging cisplatin-based combined neoadjuvant chemotherapy in advanced BC, so that P53-negative patients seemed to exhibit a more favorable response 20-22, though there have been conflicting reports 23-25. Finally, all studies regarding the role of P53 status in predicting response to radiotherapy agree on the lack of association 26-29. Moreover, in the same patients’ cohort a significantly higher recurrence and progression rate has been reported in patients with altered expression of both P53 and PRB markers as compared with those with altered expression of only one marker or with normal marker expression 8, thus supporting a cooperative effect of the two cell-cycle regulators.

In MIBC, normal PRB status has been shown to be associated with significantly higher overall survival 33, even when adjusted for P53 status and further clinicopathological parameters 34 35. Such observations reinforce the concept of multimarker panels, on the basis of the high complexity of molecule interconnections through various in vivo pathways. Multiple markers may provide better predictive information rather than single molecules, thus improving their prognostic/predictive role 36-38.

HER2

The HER2 oncogene encodes a transmembrane receptor protein whose activation results in promoting proliferation, survival, mobility and migration of tumor cells 39 40. HER2 is a pivotal parameter in the molecular subtyping of breast cancer; as a prognostic and therapeutic marker, it has been tested in several tumors 41 42. In a large cohort multi-method study of over 1000 patients, using IHC and FISH to assess HER2 status, HER2 expression by gene amplification expression has been reported in 5.1% of MIBCs 43. In a subsequent study, it has been found more commonly in lymph node metastases than in matched primary BC 44. According to a recent meta-analysis 45, HER2-positive rates in BC range from 27.8 to 85.2% in the included studies with a pooled positive rate of 41.2%; interestingly, this rate is similar to that of gastric cancer and higher than that of breast cancer 46 47. When considering more studies, the detection rate is even wider: 9% to over 80% in regards to protein overexpression and 0% to 32% regarding gene amplification 48. Heterogeneity in inclusion criteria, especially tumor stage and grade in large case series, diversity in assessing methods (gene amplification versus protein overexpression) and techniques (immunohistochemistry, in situ hybridization, PCR), lack of standardization in defining HER2 “positivity”. Moreover, ethnic or geographic differences may account for the high variability of HER2 positivity in BC reported in literature 45 49-51. Possibly due to the same reasons, conflicting data exist regarding the role of HER2 as a prognostic factor in BC 52, with reports suggesting that a HER2
amplification/overexpression has a negative prognostic value on multivariate analysis for MIBC recurrence and cancer-specific mortality. Others studies however showed no significant correlation between HER2 status and clinical outcome in both primary tumors and lymph node metastases. More promising data may come from the assessment of HER2 status in selected types of MIBC with peculiar aggressive behavior, such as micropapillary tumors.

In view of encouraging preclinical results, clinical trials are now ongoing to test the efficacy of different anti-HER2 treatment agents in patients with MIBC, as an alternative or in combination with conventional surgical and oncological therapies. These drugs span from conventional anti-HER2 molecules to their antibody cytotoxic conjugates to cytotoxic agents to tyrosine kinase inhibitors.

In NMIBC HER2 amplification/overexpression has been reported to be a significant prognosticator of more aggressive clinical behavior, especially in terms of DFS and PFS, yet conflicting data exist.

FUTURE DIRECTIONS

In the last few decades a high number of studies on putative markers has been carried out. While in prostate cancer most attention has been paid to novel markers to make the diagnosis, in BC the search for molecular markers has been oriented towards markers predicting disease outcome. A huge amount of data is available on single promising novel markers which span from hypermethylated tumor-suppressor genes to miRNA to specific protein kinase. This opens the door for the use of multivariate analysis for MIBC recurrence and poor survival in T1 bladder tumours.

The authors declare no conflict of interest.

REFERENCES


Molecular markers predicting disease outcome in bladder cancer


75 Cormio L, Sanguedolce F, Cormio A, et al. Human epidermal growth factor receptor 2 expression is more important than Bacillus Calmette-Guerin treatment in predicting the outcome of T1G3 bladder cancer. Oncotarget 2017;8:25433-41.


Lower urinary tract symptoms (LUTS) are common among elderly men and they may be linked to benign and malignant diseases of prostate and bladder, because of their shared inflammatory pathophysiology involving also the immune system. Actually the prostate should not be considered the only target of treatment in the management of male LUTS: it is necessary to treat bladder outlet obstruction, but also bladder and urethra. LUTS (particularly when refractory to therapy) often represent the starting point for identifying such conditions, requiring a specific and comprehensive approach. In this review, LUTS have been analysed with their association to the most frequent urological diseases as benign prostatic hyperplasia, prostate cancer, bladder cancer, and detrusor overactivity/underactivity, in a complex system of the elderly men.

Key words: Lower urinary tract symptoms, Benign prostatic hyperplasia, Prostate cancer, Bladder cancer, Detrusor overactivity, Detrusor underactivity, Elderly

INTRODUCTION

Lower urinary tract symptoms (LUTS) are common among elderly men and are highly widespread with significant effects on male wellness \(^1\)\(^-\)\(^3\). Extensive population studies estimate the overall prevalence of LUTS as 62.5% of men over the age of 40 and 80.7% of men over the age of 60 \(^4\).

LUTS have been related to higher morbidity and mortality \(^5\) and billions of dollars in USA annual health care expenditure \(^6\). LUTS are present in > 50% of men aged > 60 year and nearly 100% of men aged ≥ 90 year \(^7\)\(^-\)\(^8\). LUTS are usually associated with benign prostatic hyperplasia (BPH), and although BPH can produce LUTS, they can be complained without BPH. Moreover, both BPH \(^9\) and LUTS \(^10\) have been linked to the consequent risk of prostate cancer (PCa).

LUTS, BPH, and PCa are age-dependent processes \(^7\)\(^-\)\(^11\). Both a hormone-dependent pathway \(^12\)\(^-\)\(^13\) and inflammation may have a key function in the development of these processes \(^14\)\(^-\)\(^15\); accordingly, they can be treated with antihormone drugs \(^16\)\(^-\)\(^17\).

LUTS may occur independently of BPH \(^18\). Refractory LUTS are a well-recognized initial presenting symptom in a small percentage of patients with newly diagnosed bladder cancer (BC) \(^19\). Like LUTS, BPH and PCa, also BC is significantly associated with aging.

Sometime men with mixed voiding and storage LUTS after initial treatment for LUTS/BPH, show only voiding symptoms improvement, with storage symptoms persistence: in these cases the symptoms are related to bladder dysfunctions as detrusor overactivity (DO) or detrusor underactivity (DU), and deserve different approaches \(^20\). In this review, LUTS have been analysed with their association to the most frequent urological diseases as ben...
BPH, PCa, BC, and DO/DU in a complex system of the elderly men.

**LUTS AND BPH**

LUTS are traditionally classified into storage, voiding and post micturition symptoms. They are most generally correlated with an increasing incidence of bladder outlet obstruction (BOO), which mainly results from age-related BPH. Conversely BPH does not describe symptoms, but it is a histologic diagnosis with a micronodular hyperplasia and a macroscopic nodular enlargement causing BOO, partially responsible for male symptoms. In this scenario another part of responsibility is kept by the bladder and its complex neural network. As elderly women complain storage LUTS caused by DO, also men can suffer from the same storage symptoms which are the most troublesome with deep impact on quality of life (QoL). Actually the prostate should not be considered the only target of treatment in the management of male LUTS: it is necessary to treat BOO, but also bladder and urethra. The recommended medical therapy in men affected by BPH suggests α1-antagonists, 5α-reductase inhibitors and phytotherapy. Despite full dose treatment, some patient continues to be symptomatic or may show BPH progression, with recurrent urinary infections, acute urinary retention (AUR), or may need surgery. Furthermore, patient’s adherence to pharmacological therapy may be reduced because of adverse effects and patients stop taking drugs. For this reason investigators are proposing new medical strategies in the management of BPH-related LUTS: more selective α1-antagonists, phosphodiesterase 5 (PDE5) inhibitors, anticholinergics, and beta-3 adrenoceptor agonist have been introduced in clinical management of BPH, particularly in the elderly.

The most recent silodosin has equivalent efficacy compared to tamsulosin, with a lower risk of cardiovascular side effect; it may be considered a good alternative to common non-selective α1-antagonists, especially in the older patients where blood pressure modifications may cause important clinical troubles and ejaculatory dysfunctions are not really relevant. α1-antagonists, especially in the older patients where blood pressure modifications may cause important clinical troubles and ejaculatory dysfunctions are not really relevant. 

Among PDE5 inhibitors, tadalafil 5 mg is an effective and well tolerated treatment for BPH-related LUTS as well as for concomitant erectile dysfunction; it reduces significantly International Prostate Symptom Score (IPSS) score improving patients’ QoL, with no significant increase in Qmax. In case of PDE5 inhibitor’s prescription, physician should consider carefully the risk of systemic vasodilation and cardiac failure in elderly patients with pre-existing cardiac insufficiency. Likewise concomitant treatment with nitroderivates is an absolute contraindication to PDE5 inhibitor’s use.

Recently, bladder dysfunctions such as DO and DU have been revealed to play important roles in LUTS especially in the elderly men. Several studies have established that atherosclerosis and consequent chronic pelvic ischemia of the bladder may be a reason of LUTS in evolving age. Experimental models with rabbits and rats have proved that chronic pelvic ischemia produces bladder ischemia; when this process is protracted, morphological and functional alterations in bladder innervation, urothelium, detrusor muscle, and the endothelium of local microvessels may occur. Remarkably, studies with these models reveal that the duration and grade of organ ischemia are important to the kind of bladder dysfunction: moderate ischemia is associated with DO, while severe and long-term ischemia would result in DU. The IPSS voiding to storage subscore ratio has been proposed as a guide for initial treatment of men with mixed voiding and storage symptoms. In order to achieve the real pathophysiology for the persistent storage LUTS, a urodynamic study is mandatory. The AUA and EAU guidelines recommend pressure flow studies as an optional test if patients with LUTS and BPH are planning to undergo surgery; similarly antimuscarinic drugs should be prescribed in men with BPH with residual storage symptoms after treatment with α1-antagonists. Jiang et al. studied 614 men ≥ 40 years of age with LUTS and an IPSS of ≥ 8 and evidenced that LUTS does not correlate with bladder or bladder outlet dysfunction, and prostate size does not relate to symptoms or BOO sufficiently, especially in men with persistent storage LUTS after initial treatment for LUTS/BPH. In these cases an antimuscarinic drug or beta-3 adrenoceptor agonist is recommended for treatment of DO or DU. Video-urodynamic studies should be always performed for determining the specific differential diagnosis causing LUTS when patients still have storage symptoms. Only men who do not respond to the combination medical treatment and that are verified to have BOO should be referred for surgery. It is possible that storage symptoms may occur primarily or secondarily to BOO or BPH; therefore, combined treatment is favourable and can reduce LUTS after the initial medical treatment.

Numerous trials have investigated the efficacy and safety of an antimuscarinic drug in patients with persistent storage symptoms already in treatment with an α1-antagonist. The TIMES study included 879 men with symptoms of BPH and OAB: patients were randomized and received either tolterodine 4 mg ER + tamsulosin, one of the two drugs alone or placebo.
and after 12 weeks, in the combination arm the patients showed significant reduction in urgency incontinence episodes (-0.88 vs -0.31, p = 0.005), frequency (-2.54 vs -1.41, p < 0.001) and an improvement of QoL. The rate of AUR was low for the combination (0.4%) and the tolterodine arm alone (0.5%), though higher than for placebo and for tamsulosin alone 44. MacDiarmid et al. 45 reported a significant improvement of both storage and voiding symptoms (p = 0.006) in men affected by BPH treated with tamsulosin + oxybutinin 10 mg, with a non-significant increase in post-residual volume (PVR) in treated patients compared to placebo. Analogously, in the VICTOR study 46, 398 men were randomized and received tamsulosin plus either solifenacin 5 mg or placebo: in the solifenacin group, patients demonstrated a significant reduction of urgency episodes (-2.18 vs -1.10, p = 0.001) but a non-significant decrease of frequency (-1.05 vs -0.67, p = 0.135) 46. In the first two trials the most recurrent adverse event related to antimuscarinics was xerostomia; increased PVR, although statistically significant in many studies, often did not result in a significant rise in the risk of AUR requiring catheterization 44 45.

As a matter of fact, during antimuscarinic therapy, BPH patients (particularly in the elderly) should be closely monitored for PVR 25 and in the elderly great care by the physician is crucial, as cognitive deterioration may be a severe side-effect of these drugs, considering that 16% of patients > 70 years already show cognitive impairment 47. In this regard, cholinergic activity of the brain (in particular M1 and M2 receptors which characterize over 60% of the brain cholinergic receptors) is fundamental in cognitive function 48.

The only antimuscarinic which was given a favourable safety profile in the elderly is fesoterodine, since this drug was investigated particularly in the aging population 49-51. In the SOFIA trial 581 patients > 65 years (of which 33% were > 75 years old and under several drugs) were included in a 3 month double-blind randomized trial of fesoterodine versus placebo 49. At 12 weeks, patients in the treatment group showed decreased urgency (-3.8 episodes), frequency and nocturia (-0.55 episodes) (all p < 0.001) compared to placebo. Fesoterodine presented an equivalent rate of adverse events compared to placebo (39.8 vs 36.1%), mainly mild xerostomia; about the cognitive function (assessed by the mini-mental status examination) no clinically significant modifications were reported in both groups. This result may be due to the high affinity of fesoterodine for the M3 receptor and its incapacity to pass the blood-brain barrier 52.

**LUTS and Prostate Cancer**

Prostate cancer (PCa) is the most frequent solid malignant neoplasm among men in the United States 53, and one of the most common in the world 54. The incidence rises in an age-dependent way and with evidence of PCa at autopsy of almost every man in advanced age 55.

Researchers have long investigating whether there is a biologic association between BPH, LUTS and PCa or not 56-59. BPH and LUTS have not been considered risk factors for development of PCa 56-59. Actually, the Prostate Cancer Prevention Trial (PCPT) pointed out there was no association between LUTS and PCa 59.

On the other hand, a large recent population-based European study established a clear association between LUTS and the subsequent risk of PCa with hazard ratios (HR) ranging from 2.2 to 4.5 50. These numbers of relative risk (RR) are as high or higher than more traditional risk factors such as family history (RR: 2-4), race (African American vs white, RR: 1.3), prostatitis (RR: 1.5), obesity (RR: 1.05), and sexually transmitted diseases (RR: 1.5) 60. Nevertheless the European study did not use a standardized measurement of LUTS and was not capable to assess whether the association between clinical LUTS and PCa incidence was related to detection bias or not.

If an association between LUTS and PCa exists, a relevant number of men would develop PCa independently on treatment of LUTS. Weight J et al. 61 evaluated the effect of LUTS on subsequent PCa testing and diagnosis, studying prospectively a cohort of 1922 men (aged 40-79 years) with interviews, questionnaires, and abstracts of medical records for prostate outcomes. They pointed out that a possible cause of the association between LUTS and PCa is the increased “diagnostic intensity” among men whose LUTS attract the attention of physicians; however, augmented symptoms alone were not associated with intensity of testing or diagnosis 61.

A recent study pointed out that the IPSS is an independently inverse predictor of the risk of being diagnosed with PCa 62. Similarly, other LUTS-related parameters have been investigated. Prostate volume, which is directly correlated to BPO, has been shown to be inversely correlated with the risk of harboring PCa 63 64. We recently demonstrated that peak flow rate (PFR) and post-void residual (PVR) independently predicted the risk of being diagnosed with PCa 65 67 and constructed a novel nomogram based on such BPO-related parameters providing significant predictive accuracy for overall PCa (0.768) and clinical significant PCa (0.8002) 67.

It is therefore intuitive that LUTS prompts not only PSA testing but also evaluation of easily available BPO-related parameters. In clinical practice, however, physicians tend to be reluctant to advise PSA testing in men > 75 years as well as to recommend prostate biopsy for increased PSA levels; this is even more true for those
with PSA in the grey zone (4-10 ng/ml) who suffer from LUTS. Such reluctance is likely due to the perception of most PCAs in the elderly being clinically insignificant. Therefore, together with improvements in prostate biopsy technique, great efforts are currently made to identify novel markers that can improve the detection of clinically significant PCAs. Indeed, PCAs overdiagnosis may lead to too aggressive treatments with their risk of procedure-related complications. Therefore, like for other common benign urological conditions, the final clinical decision has to rely on wise clinical judgment.

LUTS and Bladder Cancer

Bladder cancer (BC) is the ninth neoplasm in worldwide cancer incidence and the seventh most common malignancy in men and seventeenth in women. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females. Worldwide differences in exposure to risk factors are largely responsible for the observed variability in incidence in different geographic areas. Cigarette smoking, accounting for 50% of BC in males and 35% in females, and occupational carcinogens are the most principal risk factors for BC in Western countries. Both genders have the highest risk to develop BC within 10 years at the age of 75; for males this risk is 2.32% and for females 0.560%. In Europe, mortality rates show a substantial reduction over the last decade of ~16% in men and ~12% in women; in the USA, BC mortality rates show decreasing trends for men already since 1975 as confirmed by the SEER (Devcan 6.7.6, April 2018, National Cancer Institute, https://surveillance.cancer.gov/devcan/). When LUTS are complained, the presence of PVR in the bladder exposes urothelium to a prolonged time contact of potential carcinogens usually contained in urine. Zhou J et al. examined prospectively the risk of BC associated to severity of LUTS among 30,183 men; among them, 476 new cases of BC were diagnosed. They pointed out that males with LUTS (voiding dysfunctions, especially urinary hesitancy) had a significantly higher risk of BC (RR: 1.60, 95% confidence interval: 1.00, 2.56). Moreover, they reported a stronger association between LUTS and early stages of bladder cancer instead of later stages, which further excludes the possibility that in this study the observed positive associations were all due to reverse causation.

Usually, the majority of patients affected by BC present with gross painless hematuria, but the remaining newly diagnosed BC patients complain refractory LUTS. Up to one fourth of patients with carcinoma in situ could present with irritative storage symptoms including frequency, urgency and dysuria. In a study on 1,000 patients, frequency and dysuria (6.0%), difficult or poor stream (3.5%) and AUR (4.0%) were reported as presenting symptoms for BC though with significant co-existing (35-41%) hematuria in each of these groups. Stower et al. pointed out that the “cystitis” symptoms were referred as the primary symptoms for patients with newly diagnosed BC in 12% of patients (12/100) and “obstructive symptoms” were mentioned in 3% of patients (3/100). However, these results did not provide about oncological outcomes. Dobbs R et al. evaluated the prevalence and clinical characteristics of 14340 (4.1%) newly diagnosed BC patients who presented with LUTS in the absence of gross or microscopic hematuria. In this study the majority of patients with LUTS presented with Ta lesions, notwithstanding a higher incidence of carcinoma in situ compared to patients with other presenting symptoms. In high risk populations with significant smoking exposure and other risk factors (including elderly patients), physicians should consider a cystoscopy in patients with refractory LUTS. In a study by Weiss et al. assessing patients for refractory overactive bladder without hematuria, 8 patients were identified with bladder cancer from a total of 1,420 patients undergoing cystoscopy for a diagnostic yield of 0.6%.

However, in asymptomatic patients (including elderly), no screening for BC is currently considered mandatory by the American Association of Family Physicians (AAFP), European Association of Urology (EAU) or The American Cancer Society (ACS). Question remains whether the presence of LUTS, like other clinical variables such as cigarette smoking, may impact on treatment outcome. To our knowledge, this issue has not been specifically addressed in BC whereby attention is mainly focused on molecular markers.

Final Remarks

There is increasing evidence for a link between inflammation and development and progression of benign and malignant diseases of prostate and bladder, and this seems to be particularly true in the elderly, whereby senescence of the immune system may further contribute to such events. While this may open perspective to immune modulation of such tumors, like in other urological cancers, LUTS often represent the starting point for identifying such conditions, requiring a specific and comprehensive approach.

Conflict of Interest

The authors declare no conflict of interest.
References


Lower urinary tract symptoms in elderly men: a simple yet comprehensive approach


Kobayashi T, Mitsumori K, Kawahara T, et al. Prostate gland volume is a strong predictor of biopsy results in men 70 years or older with prostate-specific antigen levels of 2.0-10.0 ng/mL. Int J Urol 2005;12:969-75.


Unmet clinical questions in elderly patients with locally advanced and metastatic bladder cancer

G. Pezzicoli1, A. Ummarino1, F. Maddalena2, R. Villani3, E. Barret4, M. Landriscina2

1 School of Biomedical Sciences, Erasmapmax Pole, Lesina (FG), Medical Oncology Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; 2 Laboratory of Pre-Clinical and Translational Research, IRCCS, Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy; 3 Department of Clinical and Experimental Medicine, University of Foggia, Italy; 4 Department of Urology, Institut Montsouris, Paris, France

INTRODUCTION

Bladder cancer (BC) is a deadly disease with high prevalence in elderly population. Several therapeutic issues are still unsolved in the clinical management of these patients. Radical surgery with or without perioperative chemotherapy represents the best therapeutic strategy in early-stage disease even though recurrence rates are high and few therapy options are available for recurrent patients. Platin-based chemotherapy is currently the standard of care for advanced disease with a poor life expectancy of about 12 months. Novel therapeutic options, including molecular-targeted agents and immunotherapy, are under preclinical and clinical evaluation with promising results.

A major issue in BC care is the management of elderly patients, a population with relevant co-morbidities, increased risk of life-threatening toxicities and currently not receiving the best therapy options. This review summarizes literature data about treatment strategies in elderly BC patients and the relevance of geriatric assessment to categorize fit patients who can receive standard therapies from unfit patients who should be treated with extreme caution.

Key words: Bladder Cancer, Chemotherapy, Elderly patients

INTRODUCTION

Bladder cancer (BC) is the 5th most common worldwide cancer. Risk factors include smoking, family history, prior radiation therapy, frequent bladder infections, and exposure to certain chemicals. It is an age-associated malignancy, with the median age at diagnosis of 73 years. Individuals aged 75-84 years represent the largest percentage (30%) of new cases. Data collected by the National Cancer Institute (Surveillance, Epidemiology, and End Results [SEER] Program), the Centers for Disease Control and Prevention (National Program of Cancer Registries) and the North American Association of Central Cancer Registries predicted 76,960 new urinary BC cases in 2016 with an estimated 18,000 deaths in the United States only. In addition, the strong increase of elderly population is going to be a challenge for health care systems in the developed countries within few years, especially for cancer care. Therefore, BC care in elderly patients could be a real problem in daily practice and, in such a context, different approaches are under evaluation for the BC management in elderly.

Curative therapy consists in either radical cystectomy (RC), with or without perioperative chemotherapy, or combined-modality therapy (CMT) having the goal of bladder preservation through a combination of maximal transurethral resection of bladder tumor, radiation therapy (RT), and concurrent chemotherapy. The long-term survival depends upon the stage at diagnosis. The risk
of recurrence estimated by a post-RC nomogram ranges from 20% for patients with organ-confined disease to 70% for those with limited lymph node involvement. Conversely, metastatic disease remains incurable with current therapies, with a poor life expectancy of 14 months in patients who receive systemic treatments and 8 months without treatments. A major issue in the daily medical practice is the lack of reliable tools for risk assessment in the elderly population. Therefore, curative (but risky) treatments are given only to a small percentage of elderly patients. Noon et al. addressed this issue by examining the records of 3,300 BC patients diagnosed in Sheffield, United Kingdom, between 1994 and 2009. They observed that, while more than half of patients under the age of 60 usually receives a potentially curative treatment (surgery or radiotherapy), the same happens only in one third of patients aged 70-79 and in 12% of patients over 80. Moreover, patients over 70 are more likely to die of BC and have a higher rate of more aggressive tumors. The conclusion is that elderly patients are currently not receiving the best treatment options. While no treatment options are directly ruled out by chronologic age, age-related issues can impact on performance status and medical comorbidities, increasing significantly the risk of treatment-related toxicities and must be considered into decisions in order to optimally deliver patient oriented care. On the other hand, no curative treatment is to be spared in elderly patients only because of the age, if age related issues are minimal. This review summarizes the relevant literature regarding management of chemotherapy for Muscle Invasive Bladder Cancer (MIBC) and metastatic BC in the elderly population. Moreover, it discusses clinically available tools to guide management decisions in the elderly, specifically the comprehensive geriatric assessment (GA).

DEFINITION OF ELDERLY PATIENT IN BLADDER CANCER CARE

The definition of who can be considered elderly is a major issue in geriatrics. Previously, patients who were ≥ 65 years were generally considered to be part of this population, but this limit is constantly rising. Classically, the term ‘elderly’ refers to advanced chronological age, but nowadays there are more relevant factors determining treatment decisions for this cohort of patients. For example, functional status and associated comorbidities of the individual patient are by far more significant than age. The actual trend is to classify elderly patients in “fit” (who are successful ager) and “frail”. Fit patients, regardless of age, should be considered for aggressive interventions for BC, while frail patients may not benefit. The definition of a decision tool that allows a correct distinction between the two groups is an actual challenge. Fit patients have no significant functional impairments and/or comorbidities and, thus, should receive the best possible care options as often as possible. On the other end of the spectrum, frail patients demonstrate dependence in daily activities, significantly impaired mobility, relevant comorbidities, and/or at least one significant geriatric syndrome. These patients are at high risk for toxicities from cancer treatments. Decisional issues become even more complicated if we consider patients who are vulnerable and have concomitant mild functional or cognitive impairments, well controlled and nonlife threatening comorbid conditions, and/or depression. Depression in particular is often underestimated in the elderly population, probably due to its smoldering presentation. However, if a cut-off is needed, it is worth noting that most studies nowadays use 75 years of age to define elderly patients. This population has been associated with many comorbidities and a shorter life expectancy. However, it is important to remember that comorbidities and age have been found to be independent predictors of overall survival (OS) in BC patients.

CHEMOTHERAPY FOR BLADDER CANCER IN ELDERLY PATIENTS

NEOADJUVANT THERAPY

Studies have proven that cisplatin-based neoadjuvant chemotherapy (NAC) improves OS in patients with MIBC by approximately 5% at 5 years compared to radical surgery alone. Furthermore, NAC doubles the rate of pathologic complete remissions at the time of surgery from 10-15 to 30% and improves 5-year OS approximately to 85% . Therefore, based on the proven benefit and the level of evidence, NAC is the preferred approach to management for patients with MIBC who are eligible to receive cisplatin-based chemotherapy. However, in clinical practice the use of cisplatin-based NAC is limited in both the community and academic centers and this is mostly due to a misperception of the potential benefit by both physicians and patients and to the risk of increased toxicity. Thus, a coordinated multidisciplinary approach for patient’s management has been proposed to increase the daily use of NAC . This issue is even more relevant in the elderly population due to the higher risk of age-related toxicities. Thus, the incorporation of geriatric oncologists or skilled geriatricians in the administration and interpretation of the comprehensive geriatric assessment may
help to prospectively identify patients at increased risk for chemotherapy-induced toxicity 23.

In current literature, cisplatin is the cytotoxic agent with higher activity in the treatment of BC. However, in elderly patients, carboplatin is often used instead of cisplatin as first-line therapy because it is commonly perceived to have reduced toxicity in the elderly 24. However, it is important to note that this alternative approach has not the same efficacy, since, in the neoadjuvant setting, carboplatin showed a reduced response rate. Thus, cisplatin-based chemotherapy should be considered in fit elderly patients when upfront cytoreduction is needed to improve the chance of curative surgery 24-26. Conversely, a fraction of elderly patients is ineligible for cisplatin. An expert panel developed a tool for determine cisplatin ineligibility for the purposes of clinical trial development. However, these criteria fit perfectly in clinical practice and could be a reproducible standard for determining which patients are unfit for cisplatin 27. While factors like poor performance status, high NYHA classes, low Creatinine clearance or peripheral neuropathy can preclude the use of cisplatin, age alone does not appear to affect tolerability or disease outcomes based on available data. Indeed, Chau et al. reported similar rates of eligibility for definitive local therapy following cisplatin-based NAC and similar clinical outcomes in patients aged ≥ 70 years versus younger patients with MIBC (pathologic CR, overall survival, and relapse-free survival at 3 years) 28.

In conclusion, cisplatin-based chemotherapy is an appropriate neoadjuvant strategy for elderly patients who are surgical candidates and have no contraindications. Patients who are ineligible for cisplatin, but are acceptable surgical candidates should be considered for surgery alone without chemotherapy.

Inoperable elderly patients, that have organ-confined disease and could tolerate cisplatin, can be treated with cisplatin-based regimens alone or in combination with radiotherapy. Alternatively, for those who are unfit for cisplatin, the best treatment option is a regimen based on gemcitabine, mitomycin C or fluoropirimidines 29.

**Adjuvant therapy**

Adjuvant chemotherapy is widely used in clinical practice for the management of MIBC, but a consensus has still to be established on which regimen is the most effective for improving postoperative survival. A systematic review and meta-analysis of clinical trials carried on by Hyung et al. found out that the only adjuvant regimen associated with an improvement in both the progression-free (Hazard ratio, 0.38; 95% Credible Interval, 0.25-0.58) and overall survival (Hazard ratio, 0.38; 95% Credible interval 0.22-0.65) is the gemcitabine/cisplatin/paclitaxel (GCP) combination 30. This beneficial effect can be seen among all age groups. However, even if clinical improvements due to the adjuvant chemotherapy are clear, this regimen is underused in the elderly population in common practice. Leveridge et al. showed that the rate of administration of adjuvant chemotherapy is significantly lower in patients over the age of 70 (and almost non-existent in patient aged more than 80). Moreover, patients over 70 years receive a cisplatin regimen less frequently than younger patients and this is likely due to the common fear for co-morbidities in this category of patients. However, it is important to note that this choice can negatively impact on the prognosis of elderly fit patients. Hereby, the necessity for a tool that allows the selection between fit and unfit patients is a major clinical need, so that each group could receive the most appropriate therapy 4, 13.

In this scenario, the criteria suggested for neoadjuvant therapy by Galsky et al. could be a reliable tool for decision-making 27.

**Metastatic disease**

**First line therapy**

Guidelines for the management of metastatic BC strongly recommend cisplatin-based combination chemotherapy as best option in first-line systemic therapy 31. Recently, Galsky et al. published a meta-analysis about the tolerability and efficacy of cisplatin-based combination chemotherapy in metastatic disease based on data from eight Phase II and III clinical trials with a total of 543 patients. Surprisingly, no significant differences in the frequency of renal failure (grade 3-4), febrile neutropenia, or treatment-related death or median survival (12.1 months vs 12.8 months; p = 0.91)
were found in patients older and younger than 70 years of age.

Several studies were carried on in order to understand the best combination therapy in terms of risks and benefits for advanced BCs. The combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) was compared with the doublet of gemcitabine and cisplatin (GC) in a randomized Phase III study, showing comparable outcomes (median OS 15.2 vs 14 months, respectively). Noteworthy, the MVAC regimen was associated to increased rates of febrile neutropenia (14 vs 2%), grade 3/4 mucositis (22 vs 1%), and toxic death (3 vs 1%), whereas patients receiving GC reported improved performance status while on therapy, although differences between treatment arms were not statistically significant. Therefore, GC is preferred over MVAC as first-line therapy for metastatic disease in the elderly, because of its best tolerance profile. However, as said before, some elderly patients are unfit for a cisplatin regimen and can be treated with carboplatin instead of cisplatin. Consistently with results of GC versus MVAC, gemcitabine/carboplatin produced similar OS rates as methotrexate/carboplatin/vinblastine (9.3 months vs 8.1 months) and decreased toxicity in cisplatin-ineligible patients with metastatic BC.

**SECOND LINE THERAPY**

Currently, the second line treatment following the use of a platinum agent is a complex issue. Indeed, we lack of a consensus about what regimen can be the most suitable in terms of PFS and OS. In such a scenario, several studies tried to address the question about the best treatment for a metastatic patient who underwent disease progression after a cisplatin-based chemotherapy. If the progression is observed later than 12 months after the end of first-line therapy, platinum re-challenge may be considered. Obviously, the choice between carboplatin and cisplatin in the elderly needs to be considered based on the patient’s fitness. On the other hand, for patients progressing earlier than 12 months, single-agent chemotherapy, i.e., taxanes, pemetrexed, vinflunine and ifosfamide, was shown to be active and able and lack of significant toxicity.

Unfit patients (especially those with low performance status) should be treated with single agents in order to avoid toxicities, even if combination therapy could perform better. Nonetheless, the decision to proceed with any systemic therapy rather than with best supportive care alone under these conditions must be considered.

For both first and second line therapies, toxicities are an important limiting factor. Extremely helpful could be a study by Hurria et al. who identified prospectively risk factors associated with increased chemotherapy toxicity in the elderly. While age ≥ 72 years was per se a risk factor for toxicities, by far more important were low hemoglobin, low creatinine clearance and hearing impairment. Thus, based on this evidence, polychemotherapy instead of a single agent chemotherapy should also be avoided.

Considering the low clinical activity of second-line agents, participation in clinical trials should be strongly encouraged for all eligible patients with BC. There is awareness in the BC research community of the need for effective and tolerable therapies for elderly patients with BC and the importance of designing trials that do not exclude this vulnerable population.

**TARGETED THERAPIES AND IMMUNOTHERAPY**

A new hope for the treatment of advanced BC may come from recent findings. Indeed, the advancement in the field of genetic and biology allowed a better molecular understanding of BC and showed the genetic heterogeneity of this disease and the existence of subtypes that may have treatment implications.

Even though the vast majority of patients with BC cannot benefit from targeted therapies, some reports showed dramatic and prolonged responses with the mammalian target of rapamycin inhibitor, everolimus, in metastatic BC. In addition, immunotherapy with immune checkpoint blockade of programmed-death ligand 1 (PD-L1) represents a therapeutic option for elderly BC patients since these agents are highly tolerable and lack of significant toxicity. The introduction of immune checkpoint inhibitors offers real hope for patients previously unlikely to achieve a durable response, including those who are unfit for platin. The improved tolerability of immunotherapy over chemotherapy directly correlates with its targeted mechanism of action. Currently, research is ongoing to further categorize responses and define ideal patient populations. Moreover, research is engaged in evaluating novel checkpoint inhibitors even beyond PD-1/ PD-L1 plus CTLA-4, as indoleamine 2,3-dioxygenase (IDO) inhibitors, lymphocyte activation gene 3 (LAG-3), 4-1BB (CD137), T-cell immunoglobulin and mucin-domain-containing-3 (TIM-3), colony-stimulating factor 1 (CSF-1), tumor necrosis factor receptor superfamily, member 4 (OX40), and others, to address multiple pathways in immune system functioning. Thus, there is no doubt that immunotherapy will change the standard of care of BC.
CONCLUSIONS

It is widely accepted that elderly patients with BC represent a true challenge in decision-making. Many comorbidities and hidden health problems can be found in a great part of them, especially those with a smoking history. All these factors can reduce the efficacy of therapies and increase complications. Thus, the ideal conduct should consider the classification of patients in “fit” elderly, no matter what age, suitable for more aggressive interventions, and “unfit” who should be treated with more tolerable strategies. A major issue is the lack of specific literature about elderly BC patients. Clinical trials usually enroll young patients and, often, exclusion criteria rule out patients with comorbidities. Therefore, little is known regarding the safety and efficacy of standard treatment regimens in older patients, especially those who are aged ≥ 75 years and have other health issues.

A reliable decision-making tool for these patients should help to find a balance between aggressiveness of the disease, efficacy of the therapy, comorbidities and toxicities. The main problem is that medical comorbidities may increase the risk of adverse events that may decrease life expectancy rather than improve it. Comorbidities, functional impairment or mobility disability, and geriatric syndromes (including cognitive impairment) provide a reliable and accurate estimate of life expectancy as well as a comprehensive evaluation of health status. However, it should be considered that the independent effect of these factors have not been well studied in older patients with BC. Nonetheless, they have been independently associated with a higher risk of surgical complications and morbidity and mortality from chemotherapy in other cancer populations.

Commonly used geriatric assessment tools could be useful. They consist in a multiparametric assessment, which includes measurement of functional, cognitive, nutritional and psychological status, comorbidities, self-assessed health status, mobility, and social circumstances. The National Comprehensive Cancer Network Guidelines recommend that all cancer patients aged ≥ 70 years should undergo some form of geriatric assessment since this can help to identify potential dangerous conditions, previously unrecognized, that can affect treatment tolerance and efficacy. Interestingly, more attention should be paid to psychological impairment (depression, in particular) that independently correlates with worse outcomes both in surgery and chemotherapy. In addition, cognitive impairment must be carefully considered in decision making, because it has implications to consent to any form of treatment and increases risk from therapies such as surgery and chemotherapy.

In conclusion, geriatric assessment can categorize patients into three groups that correlate with life expectancy. Fit patients with no significant functional impairments and/or comorbidities should receive the best evidence-based care possible. On the other end of the spectrum, older patients who are “frail” and demonstrate dependence in basic functional tasks, significantly impaired mobility, significant comorbidities, and/or at least one significant geriatric syndrome are at high risk for toxicities from cancer treatment and should be considered with extreme caution. A third, more complex group, is composed of patients who are vulnerable and have concomitant mild functional or cognitive issues, well controlled and non-life threatening comorbid conditions, and/or depression. In these patients, targeted interventions can be implemented with the goal of improving outcomes.

ACKNOWLEDGEMENTS

We are grateful to Prof. Maria Michela Dota, English Mother Tongue Teacher, for her precious linguistic revision.

This work was supported by AIRC (Grant IG2015 Id.16738 to ML).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References


Unmet clinical questions in elderly patients with locally advanced and metastatic bladder cancer


INTRODUCTION

Bladder cancer (BC) is the ninth most common cancer worldwide. The most common risk factors for BC are smoking, male gender, age and exposure to environmental or occupational carcinogens such as arsenic, chromium, nickel and cadmium. Carcinogens may trigger BC by inducing excessive reactive oxygen species (ROS) production and oxidative stress. High concentrations of ROS are pathogenic and can cause severe damage to cell and organelle membranes, DNA, and proteins, thus leading to cancer.

There is strong evidence linking oxidative stress and BC. Serum levels of vitamins C and E, whole blood levels of antioxidant enzymes like Superoxide dismutase and Glutathione peroxidase, and serum antioxidants were found to be significantly lower in patients than in controls, whereas serum malondialdehyde levels were found to be significantly higher, indicating presence of oxidative stress in BC patients. Moreover, with advancing stage of BC, the levels of oxidative stress increase while the levels of antioxidant molecules decrease suggesting that they may be important factors in tumor development and growth. The oxidative stress is one of the key hallmarks also of the aging process and is linked to the development of numerous age-related diseases including cancer. Therefore, ROS, oxidative damage, aging, and aging-dependent diseases like cancer seem to be connected.

Mitochondria are the center of the oxidative metabolism and the principal site of ROS production. According to the “Mitochondrial free radical theory of aging”, aging is associated with progressive mitochondrial dysfunction. This process is due to accumulation of mitochondrial DNA (mtDNA) mutations and increased ROS production leading to oxidative damage to cellular macromolecules, decline in mitochondrial quality control, reduced activity of metabolic enzymes, as well as changes in mitochondrial morphology, functionality and finally to reduced respiratory chain activity and adenosine triphosphate (ATP) generation.

The risk of BC increases with age, with age-specific curves increasing steeply after the age of 50 yr. Since the population is aging, BC will become an even bigger public health challenge in the future. This review therefore aims to find a possible link between aging and BC that can provide novel opportunities for prevention and treatment of this disease.
**MITOCHONDRIA**

Mitochondria are essential organelles in all eukaryotic cells. They are the powerhouse that provides ATP for a multitude of cellular processes by the oxidative phosphorylation system. They are the hub of metabolic pathways, primary sources of ROS, regulators of apoptosis as well as signal transduction regulators, and buffers of intracellular calcium. Mitochondria contain mitochondrial DNA (mtDNA), a small DNA of approximately 16,569 bp, which codes for 2 rRNAs (12S and 16S), 22 tRNAs, and 13 proteins subunits of four of the five complexes of the respiratory chain. Mitochondria contain mtDNA mutations, and point mutations or deletions) than nuclear DNA since it is located close to mitochondrial respiratory chain, the major source of ROS in the cell. Point mutations and deletions are the two most frequent types of mutations that arise in mtDNA genome mainly due to spontaneous errors during mtDNA replication or damage repair. Not all mtDNA mutations, however, are deleterious to cells; some may result in dangerous events, others may be simple neutral polymorphisms with no important functional consequences. Moreover, it is important to know the percentage of mutant mtDNA molecules (threshold) that can lead to a dysfunction of the mitochondrial respiratory apparatus. A pathogenic mutation would need to rise up from 60 to over 95% of level to have a functional impact on the respiratory chain.

Apart from alterations of mtDNA (deletions, point mutations, and copy number), mitochondrial dysfunctions may also involve altered expression or damage of mitochondrial proteins and enzymes coded by nuclear DNA. To ensure maximal mitochondrial function, the mitochondrial quality control systems is active to protect mitochondria from ROS damage at the protein, DNA, and organelle level. At the protein level, mitochondria are protected by antioxidant systems, DNA repair, protein folding and degradation. At organelle level, damage activates mitochondrial biogenesis (de novo synthesis of mitochondria), mitochondrial dynamics (fusion and fission of mitochondria) and mitochondrial autophagy, also known as mitophagy. Mitochondrial number and shape depend on mitochondrial biogenesis and dynamics. Mitochondria continuously join by the process of fusion and divide by the process of fission. Fusion is mediated by mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2) in the outer mitochondrial membrane and by OPA1 in the inner membrane; Fission is mediated by dynamin related protein 1 (Drp1) and mitochondrial fission 1 protein (Fis1). The machinery regulating mitochondrial dynamics is highly integrated with mitophagy, with which it plays a role in mitochondrial quality control. Upon fission, mitochondria can be segregated into polarized and depolarized daughter mitochondria. While polarized daughter mitochondria can undergo fusion, depolarized mitochondria are targeted by mitophagic proteins to degradation. Mitophagy promotes turnover of dysfunctional mitochondria that would otherwise hamper the cell homeostasis. Important proteins in mitochondrial protein quality control systems are Lon protease and CLPP, two ATP-dependent protease located in mitochondrial matrix that contribute to the degradation of abnormal proteins as well as the maintenance of mitochondrial function.

**MITOCHONDRIAL ALTERATIONS IN AGING**

The mitochondrial free radical theory of aging sustains that mitochondrial ROS production increases with age because of an age-related decline of several ROS-scavenging enzymes and a decline in mitochondrial function. ROS increase leads to accumulation of mtDNA mutations, and a vicious cycle occurs because somatic mtDNA mutations impair respiratory chain function, which in turn results in a further increase in ROS production and accumulated oxidative damage to proteins, lipids, and DNA. According to this theory, mitochondrial alterations have been extensively described in aging tissues of many organs. In particular, a key reported feature of aging mitochondria was the increase in somatic point mutations and large deletions in the mitochondrial DNA (mtDNA). Since mtDNA encodes essential parts of the oxidative phosphorylation machinery, mutations of mtDNA cause oxidative phosphorylation dysfunction and a decline of cellular function. In addition, the number of mitochondria have been showed to decrease with age, thus contributing to the impaired ATP production and respiratory chain activity observed in the elderly. Altered mitochondrial dynamics was reported during aging. In particular, the fusion protein Mfn2 is repressed in muscle during aging, determining the inhibition of mitophagy and of mitochondrial quality control that lead to the accumulation of damaged mitochondria.

Age-related decline in Lon expression and/or its proteolytic activity occurs in parallel with the accumulation of damaged proteins in rat liver mitochondria isolated from aged animals suggesting that Lon is a stress-response protein playing a key role in maintaining mitochondrial function. However, an increase of Lon protease expression was reported in rat heart suggesting that its effect in aging may vary from one organ to another.

**MITOCHONDRIAL ALTERATIONS IN BC**

The best characterized metabolic phenotype of tumor cells is the Warburg effect. Many years ago Otto Warburg observed that cancer cells actively metabolize glucose and produce an excess of lactate even in the...
presence of oxygen, the so-called reverse Pasteur effect or aerobic glycolysis. He guessed that malignant cells should harbour defects in the respiratory chain of mitochondria and that cancer cells are able to increase the glycolytic rate to compensate the lower energy yield per single glucose. Also in BC the main energy source to sustain uncontrolled cells growth and proliferation is an aerobic glycolysis-dependent metabolism; indeed, BC cells display increased expression of genes coding for glycolysis, for the pentose phosphate pathway, and for fatty-acid synthesis suggesting a deficit of mitochondrial activity in this cancer.

Mitochondrial mutations have been described in BC in the form of point mutations, single-base deletions, and insertions in the non-coding D-loop region or in the coding regions for protein components of oxidative phosphorylation. In both human and rat bladder cancers, mtDNA exhibits a high rate of mutations. In particular, the repetitive sequences of mononucleotides within the mitochondrial genome are unstable and subjected to deletions. The tumorigenic role of mtDNA mutations in BC was demonstrated only for the 21-bp deletion (from nucleotide position 15,642-15,662) in cytochrome B gene. This mutation was found in neoplastic tissue and urine of a BC patient. Later on, it was shown that the overexpression of this mtDNA mutation generated increased ROS accompanied by increased oxygen consumption and lactate production and induced significant tumor growth in vitro and in vivo by triggering rapid cell cycle progression. Moreover, forced expression of this mutation induced mitochondrial proliferation and prevented apoptosis suggesting a role of TFAM in cancer progression.

The high incidence of mtDNA mutations in BC suggests that mtDNA could play an important role in the process of carcinogenesis and could represent a valuable marker for early BC diagnosis. Like for prostate cancer, markers for early detection are eagerly awaited. BC tissue has been found to display high levels of a marker of DNA oxidative damage, namely, 8'-hydroxy-2'-deoxyguanosine (OH8dG) but also altered expression of some mitochondrial proteins. Lon protease expression level was found to be significantly higher in neoplastic compared to non-neoplastic tissue. Moreover, Lon expression was found to increase with tumor grade, being low in well differentiated (G1) BC, moderate in G2 BC, and high in poorly differentiated (G3) BC, with a dramatic difference between G2 and G3 tumors. It can be envisioned that Lon up-regulation may contribute to metabolic reprogramming observed in cancer by favoring the switch from a respiratory to a glycolytic metabolism that helps cancer cell survival in the tumor microenvironment.

The fusion protein Mfn2 expression was found to be significantly lower in BC and its overexpression has been suggested to inhibit cell proliferation by arresting the transition of the cell cycle from the G1 to S phase, and to induce apoptosis. Taking findings together, Mfn2 gene seems to be a potential BC tumor suppressor gene that promotes apoptosis and inhibits the proliferation of BC cells. Moreover, the mitochondrial transcription factor A (TFAM), a mitochondrial protein required for mtDNA replication, transcription and stability was found to be significantly increased in BC cells and to be directly related to tumor stage. In the BC 5637 cell line, TFAM overexpression induced cell proliferation, migration and colony-forming ability, suggesting a role of TFAM in cancer progression.

If above-mentioned data suggest that mitochondrial dysfunctions may have prognostic role, no information is currently available regarding their potential predictive role, in other words, their ability to predict treatment response. In the last two decades, great efforts have been made to find molecular markers that can reliably predict BC response to available treatments. Most work has been done in the field on non muscle invasive bladder cancer (NMIBC), particularly high grade T1 disease whose response to intravesical instillation of Bacille Calmette-Guerin is poorly predictable by standard clinical and pathological factors. Emerging evidence suggest that the combination of immunohistochemical markers is more effective than the single ones in predicting treatment response and disease outcome. Case volume however remains an issue in this as well as in almost all fields; thus, studies with larger number of patients are eagerly awaited. Moreover, like for other common urological diseases, the decision-making process should be tailored on patient conditions as well as wise clinical judgment.

Attempts have been made to identify molecular markers that can predict response also of MIBC to available treatment options, particularly systemic chemotherapy. Markers of mitochondrial function are among novel putative molecular predictive markers. More important, there are grounds to assume they could represent novel potential therapeutic targets, and we are working to assess whether they could contribute to modulation of that immune response which is demonstrated in other urological cancers.

**CONCLUSIONS AND PERSPECTIVES**

In aging, the accumulation of ROS and somatic mtDNA mutations together with dysregulation of mitochondrial dynamics and mitochondrial quality control may induce mitochondrial functional decline contributing to age-related decline. Similarly, in BC the oxidative stress
related to smoking and to exposure to carcinogens may induce accumulation of somatic mtDNA mutations and alterations in mitochondrial dynamics and quality control, which may lead to mitochondrial dysfunction. These findings would support the hypothesis that age-related mitochondrial oxidative damage may reinforce and exacerbate the oxidative damage due to smoke and carcinogens and this may be one possible explanation for the increased risk of BC in elderly or even for its trend to recur in smokers. If this is true, it is attractive to assume that improving mitochondrial function by antioxidant supplementation could be useful to prevent BC as well as to increase response to available treatments.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

References
2. Lee GH, Yu HS. Role of mitochondria, ROS, and DNA damage in arsenic induced carcinogenesis. Front Biosci (Schol Ed) 2016;8:312-20.
Radical cystectomy and orthotopic neobladder in fit octogenarians

B. Calò¹, E. Carvalho-Dias², R. Autorino³

¹ Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy; ² Urology Department, Hospital de Braga ICVS, University of Minho, Braga, Portugal; ³ Division of Urology, Department of Surgery, VCU Health, Richmond, VA, USA

INTRODUCTION

In industrialized countries, the average life expectancy has continuously increased during the last decades and this trend is expected to continue. Bladder cancer (BC) affects old patients, particularly smokers, and average age at diagnosis is approximately 70 years. Nearly 25% of patients present with muscle invasive bladder cancer (MIBC) and a significant number of those presenting with non muscle invasive disease will progress to MIBC over time.

Radical cystectomy (RC) with pelvic lymph node dissection is the standard of care for patients with muscle invasive bladder cancer (MIBC). Nevertheless many elderly patients are often considered unfit for such major surgery. Indeed, only 10-20% of octogenarians with MIBC undergo RC due to the perception they would not tolerate RC and urinary diversion because of age and comorbidities. Recent reports, however, have shown that RC can be safely performed in elderly individuals with low perioperative mortality, acceptable morbidity and in most cases without significant complications. Age is not an absolute contraindication to neobladder construction providing adequate cognitive status and absence of major comorbidities.

Background and aims. Octogenarians are usually considered poor candidates to orthotopic neobladder after radical cystectomy. Herein we report our experience with feasibility, efficacy and safety of orthotopic neobladder in octogenarians.

Patients and methods. Two 83 year-old patients with muscle invasive urothelial carcinoma were considered eligible for orthotopic neobladder following radical cystectomy. Their cognitive status was excellent; no serious comorbidities. Follow-up consisted of chest/abdomen computed tomography every six months for three years, then yearly. Urinary continence was assessed recording day-time and night-time used-pad and International Consultation on Incontinence Questionnaire (ICIQ).

Results. Final pathology was high-grade urothelial carcinoma (pT2N0) in patient A and high-grade urothelial carcinoma with neuroendocrine component (pT3N1) plus prostate adenocarcinoma Gleason 3+3 (pT2a) in patient B. No complication occurred. However, patient B progressed (bone metastases) after 3 months and died 7 months after surgery due to the aggressive behaviour of the neuroendocrine tumor. Patient B presented 74 months after surgery with a 3.5 tumor of the left renal pelvis. He refused further surgical treatment and died 13 months later due to metastatic disease. Patient A scored 12 at 3 month ICIQ as he needed 1 pad day-time and 1 night-time but experienced progressive improvement up to full day-time continence and safety liner night-time, scoring 2 at 1-year ICIQ. Early functional outcome was good in patient B who was continent day-time but used 1 pad night-time. His ICIQ score was 6.

Conclusions. Age is not an absolute contraindication to neobladder construction providing adequate cognitive status and absence of major comorbidities.

Key words: Bladder cancer, Cystectomy, Neobladder, Octogenarian, Aging
deviations from routine postoperative care. An ileal conduit is usually the urine diversion of choice in elderly patients but it has recently been shown that an orthotopic neobladder can be carried out with no additional complications compared with an ileal conduit.

Herein we describe the outcomes of two octogenarian patients (83 years) who underwent RC with orthotopic neobladder construction.

**PATIENTS AND METHODS**

We performed radical cystectomy with orthotopic urinary diversion in two octogenarian patients with excellent cognitive status, good clinical conditions and strong motivation for a continent urinary diversion. Patient A was a 83-year-old man who presented with hematuria an a bladder ultrasound showing a 3 cm mass of the right lateral bladder wall. Transurethral resection of the bladder tumour (TURBT) revealed high-grade papillary urothelial carcinoma of the bladder extensively infiltrating the bladder muscle (pT2). Chest/abdomen computed tomography (CT) pointed out no sign of metastases; thus, he underwent a Y-stapled ileal orthotopic neobladder. Patient B had a similar history: hematuria, 3.6 cm bladder mass at ultrasounds and TURBT showing high-grade papillary urothelial carcinoma of the bladder extensively infiltrating the bladder muscle (pT2). Chest/abdomen CT pointed out no sign of metastases; thus, he underwent a W-stapled ileal orthotopic neobladder.

Oncological follow-up included chest and abdominal CT every six months until the third year and then yearly to rule out upper tract or metastatic disease. Functional outcome in terms of urinary continence was assessed at 1 month, 3 months and then yearly by day-time and night-time used-pad and International Consultation on Incontinence Questionnaire (ICIQ).

**RESULTS**

Postoperative course was uneventful; patient A was discharged on 18th postoperative day and patient B on 16th with no catheter, splint or drain. Final pathology revealed, in patient A, high-grade urothelial carcinoma extending to deep bladder muscle (pT2N0); in patient B, conversely, it revealed high-grade urothelial carcinoma with 30% of neuroendocrine pattern extending to the perivesical fat and metastatic to 2 obturator nodes (pT3N1). There was also a pT2a Gleason 3+3 prostate adenocarcinoma, despite he had undergone prostate biopsy 22 month earlier under our protocol. Patient B refused adjuvant chemotherapy. Both patients regularly attended follow-up with the urinary continence specialist nurse. At 1-month follow-up, patient A reported day-time and night-time incontinence with usage of 6 pads/day; his ICIQ score was 18; patient B reported mild day-time incontinence but night-time leakage, with usage of 4 pads/day, his ICIQ score was 12. At 3-month follow-up, patient A reported 1 pad day-time and 1 pad night-time; his ICIQ score was 12 and at 1-year follow-up he had experienced progressive improvement up to full day-time continence and safety liner night-time, scoring 2 at ICIQ. Patient B reported, at 3-month follow-up, day-time continence but use of 1 pad night-time. His ICIQ score was 6. Unfortunately, total-body CT scan showed multiple bones metastasis. He again refused chemotherapy and died 7 months after surgery for metastatic disease. Unfortunately, immunotherapy, which has been shown to yield promise in other urological cancers, was not available in those days.

Oncological follow-up in patient A was negative but at six-year annual follow-up (74 months after surgery) CT scan showed a 3.5 tumor of the left renal pelvis. He refused further surgical treatment and died 13 months later due to metastatic disease.

**DISCUSSION**

In most clinical conditions, the role of age in planning treatment and determining its outcome is controversial. As for RC, there is evidence that very elderly patients have a high risk of perioperative morbidity and mortality. Specifically, the 30-day mortality rate in octogenarians reaches 14%, being significantly higher than that of younger patients. Zattoni et al. though reporting that perioperative complication rates ranged from 11 to 67% in patients aged > 80 years, concluded that age alone did not represent a contraindication. One of the most important determinant of complications is the type of urinary diversion. In a recent study analysing the impact of perioperative complications in patients aged > 75 years, major complications were reported in 27% of patients who underwent ileal conduit and in 36% of those who received cutaneous ureterostomy. Patrick et al. reported that overall survival was the best in patients who received an orthotopic neobladder, followed by those who had an ileal conduit, while it was worse in those who had cutaneous ureterostomy. Of course these findings reflect patient selection, suggesting that the fittest patients received orthotopic neobladder while those in the worst general conditions received ureterocutaneous. Accordingly, our strategy is to offer ureterocutaneous to those who are not fit enough for an orthotopic neobladder.
We almost abandoned ileal conduit on the assumption that if a patient is fit enough for an ileal conduit (involving an ileal resection) than he is fit enough for an ileal orthotopic neobladder providing a viable urethra. The present experience confirms that also well-selected octogenarians can safely be offered an orthotopic neobladder after RC. Cognitive status, motivation and specific support by dedicated continence nurse remain key issues in managing such patients as urinary continence is a key point in determining patient's satisfaction after this procedure. Sogni et al. obtained day-time and night-time complete continence rates of 56 and 25%, respectively, in a cohort of patients 75y.

An emerging issue is the role of robotic RC and orthotopic ileal neobladder in the elderly; the advantage of reduced invasivity is counterbalanced by length of the procedure and pneumoperitoneum. Moreover, potential complications associated to specific procedural steps should be taken into account.

Finally, other 3 factors deserve attention. First, like for other common urological diseases, treatment should be tailored to patient local and clinical conditions and be based on wise clinical judgement. Second, case volume, which is proved to be true for RC and ileal neobladder as for many other surgical fields. Third, tumor biological behaviour, as factors predicting disease outcome are proving to become more and more reliable.

In conclusion, our two cases show that RC with orthotopic ileal neobladder is feasible in well-selected octogenarians. Good functional outcomes can be obtained provided good cognitive status and motivations as well as specialized continence support.

Conflict of Interest
The authors declare no conflict of interest.

References
15 Wuehrich PY, Vidal A, Burkhard FC. There is a place for radical cystectomy and urinary diversion, including orthotopic bladder substitution, in patients aged 75 and older: results of a retrospective observational analysis from a high-volume center. Urol Oncol 2016;34:19-27.


