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INSIDE

Review of

EAU 2018

Copenhagen, Denmark

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"...we are all immensely proud of EMJ Urology 6.1 and are sure that the fascinating content will spark countless hours of intense debate and discussion..."

Spencer Gore, CEO

Editorial Board

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Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

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- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

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This Publication

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Masthead

European Medical Journal 3.1

EMJ leaps into March with the year's first edition of our flagship publication. This edition is packed with an assortment of peer-reviewed articles from a body of therapeutic areas.

VIEW ALL JOURNALS ←

Welcome

A very warm welcome to *EMJ Urology 6.1*, an eJournal dedicated to the dissemination of high-quality peer-reviewed articles that detail the very latest developments, research findings, and key issues within urological medicine. Alongside these articles are, as always, EMJ's comprehensive review of the European Association of Urology (EAU) Congress, sharing the highlights of the 4-day event; abstract reviews penned by the authors themselves; and interviews with esteemed members of the *EMJ Urology* Editorial Board.

The Annual EAU Congress welcomed >10,000 attendees to the Danish capital Copenhagen, but there was no time to see the sights as the EAU organised a fantastic scientific programme that covered a plethora of hot topics within urology. Complementing the brilliant panel sessions were a myriad of abstracts and posters detailing the results of pioneering research, a select number of which are summarised within the journal. *EMJ Urology 6.1* also contains two fascinating interviews with world-leading experts who give their opinions on key issues within the field and offer the next generation of physicians advice for the future.

The entire team here at EMJ is delighted to share with you a selection of the highest quality peer-reviewed articles urology has to offer. In this edition's Editor's Pick, da Silva et al. evaluate the conventional treatments of bladder cancer, a disease of growing concern within the field, and proceed to detail and discuss novel groundbreaking therapeutics, including the use of nanoparticles for targeted and sustained drug release. This captivating article considers how bladder cancer therapeutics have developed, while also making it clear that there is always room for improvement. Continuing the theme of urological oncology, Babu and Sahasrabudhe consider the personalisation of prostate cancer care. Prostate cancer is the second most commonly diagnosed cancer in men and 30% of patients require surgery, making it a key issue for the field. The authors consider less invasive therapies that allow for targeted personalised cancer therapy. Moving away from urological malignancies, this edition also details a plethora of other fascinating topics; for instance, Irekpita et al. evaluate the role of retrograde urethrography in the diagnosis of urethral stricture.

With plenty to offer, we are all immensely proud of *EMJ Urology 6.1* and are sure that the fascinating content will spark countless hours of intense debate and discussion, which will no doubt lead to further developments and breakthrough discoveries in the treatment of urological disorders. We already look forward to joining you all in Barcelona, Spain for 2019's EAU Congress!

Spencer Gore

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear friends and colleagues,

As Editor-in-Chief of *EMJ Urology*, I am extremely honoured to present to you the 2018 edition of this exceptional eJournal. Included within are both high-quality peer-reviewed articles and a much-anticipated, comprehensive review of the European Association of Urology (EAU) Congress 2018, which was in the beautiful city of Copenhagen, Denmark.

With the theme of patient involvement highlighted throughout many aspects of the 2018 EAU Congress programme, now is a particularly prominent time to focus on enhancing the quality of life of urological patients across the globe. Many examples of the vital work that is currently underway were presented at this year's meeting and are described within the Congress Review section for your reading pleasure. Through advanced diagnosis, treatment, and management of urological conditions, as detailed in the abstract reviews and original articles within this issue, we must work together to reduce the stigma associated with these diseases and bring patient involvement in line with that of other medical disciplines.

My Editor's Pick for *EMJ Urology 6.1* is provided by da Silva et al., who commented on the need for efficient and well-tolerated treatment approaches to improve the quality of life of bladder cancer patients, an example of a challenging urological condition. New therapeutic approaches using innovative strategies, such as nanoparticles, are discussed in detail within this fascinating review.

With prostate cancer a leading cause of cancer-related death among men, personalised treatment for the condition is another area of significant unmet need. Babu and Sahasrabudhe review the strategies currently under investigation for the personalised management of prostate cancer, including circulating tumour cells, poly(adenosine diphosphate-ribose) polymerase inhibitors, and the emerging role of genomic assays. In another comprehensive review, Chokalingam et al. assess the currently available literature on cell-based tissue engineered substitutes for urethral reconstruction, touching on the complex clinical issues and future directions for yet another demanding area of urology. These are just a few examples of the groundbreaking insights revealed within.

On behalf of the *EMJ Urology* Editorial Board, I would like to thank all authors and peer reviewers for their contributions to this publication, and I hope readers take pleasure in discovering the insightful and thought-provoking content.

Kind regards,

Dr Abdullah Erdem Canda

Yildirim Beyazit University, Turkey

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Featured inside:

Feature

+ How I Diagnose Hypereosinophilic Syndromes
  Simon Kavanagh, Jeffrey H. Lipton

Symposium Review

+ Management of Multiply Relapsed Aggressive Non-Hodgkin Lymphoma: New Perspectives

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+ Editor's Pick: Renal Involvement in Multiple Myeloma
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+ Peyronie's Disease: Recent Treatment Modalities
  Ali Can Albaz, Oktay Üçer
+ Significance of Asymptomatic Bacteriuria Jharna Mandal
+ The Role of Selective Serotonin Reuptake Inhibitors in Premature Ejaculation Alka Aggarwal et al.
+ Do Preoperative Alpha Blockers Facilitate Ureteroscope Insertion at the Vesico-Ureteric Junction? an Answer from a Prospective Case-Controlled Study Ashok Kumar Sokhal et al.

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Congress Review

Review of the European Association of Urology (EAU) 33rd Annual Meeting 2018

Location: Copenhagen, Denmark – Bella Center

Date: 16.03.18–20.03.18

Citation: EMJ Urol. 2018;6[1]:12-26. Congress Review.

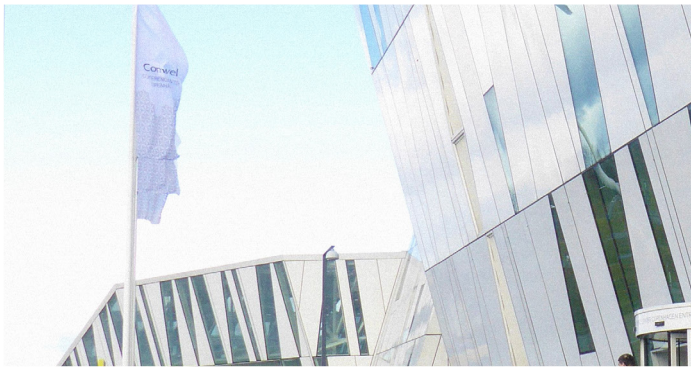
March saw >10,000 members of the global urological community travel to the Danish capital Copenhagen to attend the Annual European Association of Urology (EAU) Congress, Europe's largest urological event. The drumrolls of anticipation were literal as the opening ceremony was kicked off with a pulsating performance from the Copenhagen Drummers, who first hit the headlines with their triumph in the 2010 edition of Denmark's Got Talent. When the thunderous applause had finally ceased, the EAU Secretary General, Prof Christopher Chapple, took to the stage and welcomed all attendees. He announced: "As you can see, the EAU meeting has grown every year and it is fantastic to see such an attendance. I bring you greetings from the Executive and Board of the EAU, and we warmly welcome you here, and it is through working with you that we are able to achieve what European urology has achieved in recent years."

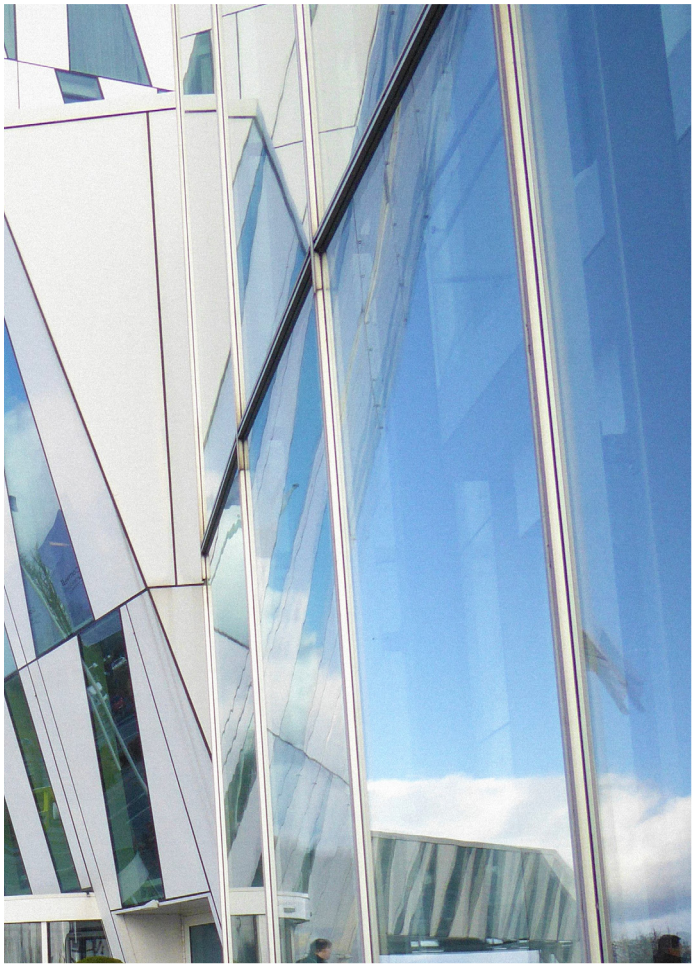
Indeed, the ability to leverage the diverse experience and knowledge of the medical professionals in attendance was a highlight of the scientific programme. There were numerous live surgery sessions, which enabled delegates to witness how particular procedures were carried out and learn more about specific aspects of a procedure that they might be finding difficult; these live surgery sessions also facilitated the consistency of standards across Europe and the globe. The debate sessions also offered not-to-be-missed opportunities; indeed, the EAU organising committee had made a special effort this year to increase the number and length of these sessions. The cut and thrust of the lively verbal sparring, debating key urological issues, enabled a vast number of ideas to be shared throughout the congress. Commenting on the debate sessions, Prof Arnulf Stenzl, Chair of the Scientific Congress Committee, enthusiastically explained: "[Medical professionals] can get a lot via video streaming, but these debates, sometimes even participating in that debate, that is something they can only do here, and that should be a good reason to come here in person."

As ever at the EAU Congress, there were numerous awards bestowed. The EAU Frans Debruyne Lifetime Achievement Award was presented to Prof Didier Jacqmin by Prof Chapple, and the EAU Crystal Matula Award was awarded to Prof Selcuk Silay. First prize for a non-oncology-related abstract was presented to Chebbi et al. for their work, which concluded that conservative management should be considered an option for patients with renal trauma associated with urinary extravasation at the initial assessment with computed tomography (CT). The prize-winning urology-related abstract, authored by Birtle et al., was on the topic of post nephroureterectomy treatment for upper tract urothelial cancer. This year's EAU Congress also saw the culmination of an exciting new competition: the EAU Guidelines Cup. As one might expect from the award's title, this was a contest to crown the EAU member with the most comprehensive knowledge of the EAU Guidelines. By the time of the congress, 450 entrants had been whittled down to just 3. These 3 took to the stage to face off in one final quiz. When the dust had settled, Dr Dimitrios Deligiannis, ably supported by Team Greece, emerged victorious and claimed the top prize: free attendance at any of the masterclasses offered by the EAU.

"I bring you greetings from the Executive and Board of the EAU, and we warmly welcome you here, and it is through working with you that we are able to achieve what European urology has achieved in recent years."

Overall, the EAU Congress provided a urological experience par excellence, with countless opportunities to network, learn, and share ideas. The EMJ team was privileged to be part of this event, and we are very much looking forward to visiting Barcelona in 2019 for the 34th Annual EAU Congress!





A New Drug to Combat Kidney Stones

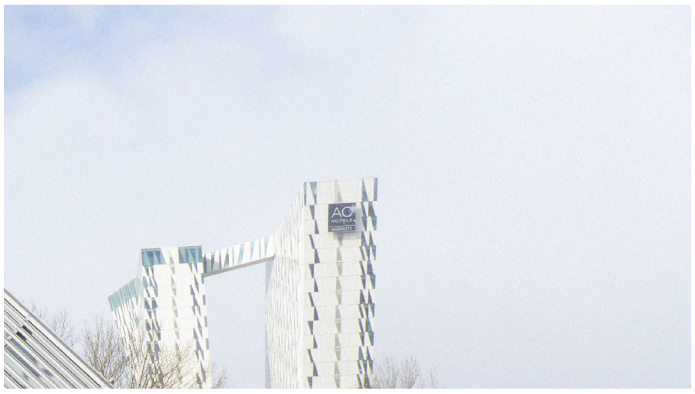
KIDNEY STONES affect 50–60 million Europeans, according to estimates made by the European Association of Urology (EAU). A new Japanese study, reported in a EAU press release dated 17th March 2018, has revealed that a β3-adrenergic receptor agonist, which regulates fat accumulation, prevents the formation of kidney stones in mice, offering a new avenue for treatment options.

Free fatty acids induce inflammation and other cytotoxic events that promote kidney stone formation. β3 agonists, commonly used in weight management therapies, trigger the conversion of white fat cells into beige fat cells that reduce the levels of free fatty acids. Therefore, it was hypothesised that, with the use of β3 agonists, the level of free fatty acids could be reduced and the formation of kidney stones prevented; these drugs will therefore offer an improved universal preventative therapy over the potassium-sodium citrate drugs currently used.

For 12 days, 20 experimental mice received daily intra-abdominal injections of the β3 agonist CL316243; control mice were injected with saline for the same time course. At Day 6 both populations were also initiated on daily injections with glyoxylate, an agent that promotes the formation of kidney stones. Kidney stone formation was shown to decrease to 17% in the experimental group, significantly lower than the control group (p=0.05). Analysis of the adipose tissue identified significant differences between the two gene expression profiles, including a 4.2-fold increase in adiponectin, a protein key to fatty acid breakdown, in the experimental mice.

"I believe that this may open the way to the development of the new drugs which can stop the development of kidney stones in at-risk people."

Dr Teruaki Sugino, Graduate School of Medical Sciences, Nagoya City University, Nagoya City, Japan, commented on this proof-of-concept study: "I believe that this may open the way to the development of the new drugs which can stop the development of kidney stones in at-risk people." The study cannot yet be directly translated into humans and requires further work in animal models to test tolerability and efficacy, but the use of β3 agonists to prevent kidney stones presents a new dawn in medical treatment.



Gender Reassignment Surgery Improves Quality of Life

One of the largest clinical surveys assessing the effect gender reassignment surgery has on quality of life (QoL) has shown a distinct improvement in general and trans-specific QoL after male-to-female reassignment surgery. According to a EAU press release dated 17th March 2018, the novel trans-specific Essen Transgender Quality of Life Inventory (ETLI) was shown to give the best assessment of QoL post reassignment surgery available to clinicians.

Generally, transgender people have a worse QoL than the non-transgender population, with elevated stress levels and mental illness. The presentation of ETLI at the 2018 EAU Congress is encouraging for both clinicians and the transgender community and presents the first available method to accurately assess wellbeing after surgery.

Dr Jochen Hess, University Hospital Essen, Essen, Germany, led the research team that followed 156 patients for >6 years after gender reassignment surgery and used the specifically designed ETLI to explicitly evaluate patient QoL. There are an estimated 1.4 million adults identifying as transgender in the USA, equating to roughly 0.6% of the population, which further emphasises the importance of being able to quantifiably evaluate the benefits of gender reassignment surgery.

"...we now have the first specific validated tool for measuring QoL in transgender patients, we hope that this means that we can go forward to gather better information to help us improve treatment."

The results of the study were largely positive, with 75.0% of participants reporting they experienced a strong enhancement of general life satisfaction, and 67.1% were satisfied with their physical appearance as a woman. Both optical and functional results were also encouraging, with 71.0% and 65.3% reporting to be (very) satisfied, respectively. Additionally, 76.2% of patients confirmed they were able to achieve orgasms.

Despite the high dropout rate, due in part to participants not being interested in taking part, Dr Hess was positive about the future impact of ETLI, commenting: "Nevertheless, we now have the first specific validated tool for measuring QoL in transgender patients,

we hope that this means that we can go forward to gather better information to help us improve treatment."

Call for Greater Focus on Psychological Care for Cancer Patients

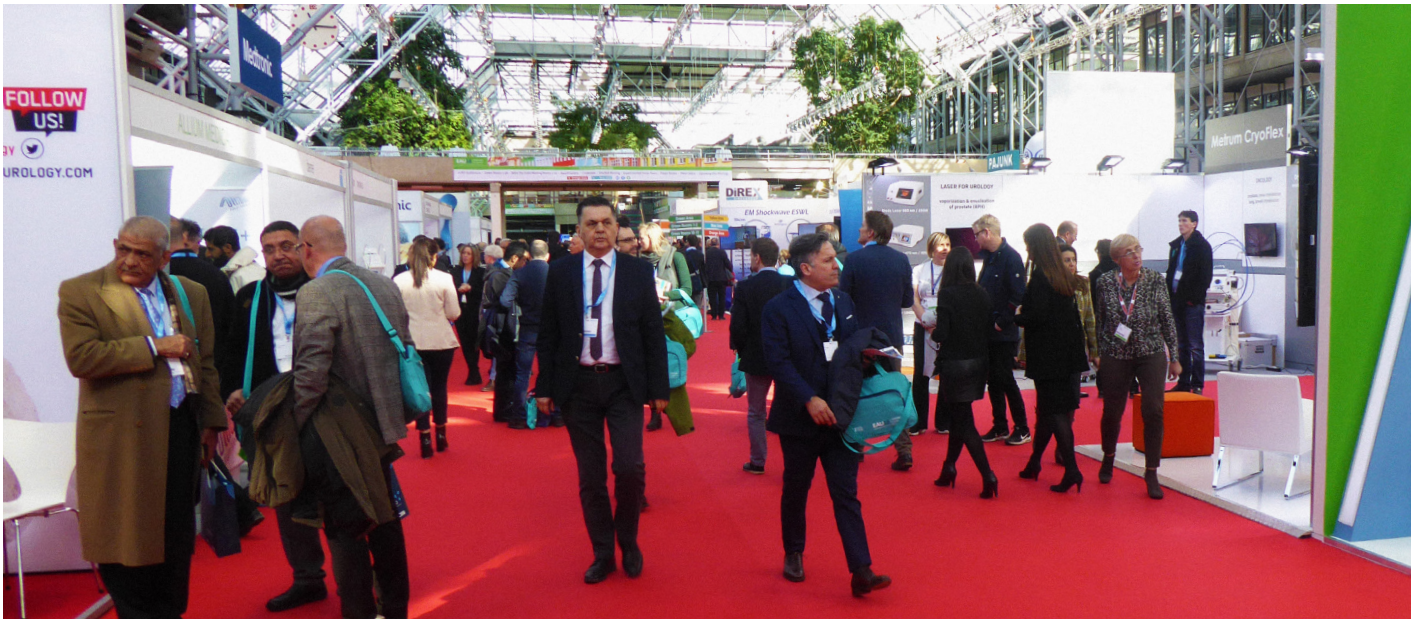
CHANGES to the paradigm of urological cancer management have been suggested following the results of a study reported in a EAU press release dated 16th March 2018. The researchers reported that patients with urological cancer were significantly more likely to commit suicide than those individuals without cancer, suggesting that management of psychological stress should form an essential component of the management regimen for urological cancer.

It is already known that psychological stress affects cancer patients, with 5–25% of patients affected by depression; therefore, this study, the first major examination into suicidal intent in cancer patients, provides valuable information for urologists in designing management strategies.

The researchers conducted a retrospective analysis of all patients from England and Wales in the Hospital Episode Statistics database who had been diagnosed with cancer from April 2001–January 2011. The headline finding was that patients with urological cancers were 63% more likely than other cancer patients to commit suicide and 5-times more likely than individuals without cancer. The suicide incidence was 48 per 100,000 for patients with bladder cancer, 36 per 100,000 for patients with kidney cancer, and 52 per 100,000 for patients with prostate cancer. The results also highlighted that the urological cancer with the shortest median time to suicide, 175 days, was kidney cancer. No difference in suicide rates was found when results were adjusted for sex; however, those patients with kidney cancer aged <50 years were more likely to attempt suicide ($p=0.01$), and older patients with bladder and prostate cancer were more likely to attempt suicide ($p<0.01$). Further analyses showed that there was no association between the Charlson Comorbidity Index and suicide attempts in patients with prostate or bladder cancer.

"Formal identification of those at risk [of developing suicidal intentions] and early intervention should form the standard of care for patients diagnosed with urological cancers."

The researchers wrote: "Formal identification of those at risk [of developing suicidal intentions] and early intervention should form the standard of care for patients diagnosed with urological cancers." This work has revealed several management avenues to be considered. For instance, the difference in median time to suicide between cancers suggests that there may be times of particular psychological vulnerability for patients where intervention would be most efficacious.



Important PIVOT Trial Results do not Represent Real-World Patients

CONCLUSIONS drawn from the influential prostate cancer study PIVOT have had a major impact on clinical decision-making, both in the USA and worldwide. Now, a new analysis performed by researchers at the Henry Ford Hospital, Detroit, Michigan, USA, suggests that the subject group examined in PIVOT may not accurately reflect real-world patients.

PIVOT included 731 men with low, intermediate, or high-risk prostate cancer, for almost 20 years; these patients had a median prostate-specific antigen value of 7.8 ng/mL and were randomised to radical prostatectomy or observation. Results indicated that there was little difference in overall mortality in patients undergoing surgery compared to those managed through observation only, though the latter group did report more side effects.

However, a research team from Henry Ford Hospital used data from three USA cancer databases to assess whether PIVOT accurately reflected real-world patients; these registries were the Surveillance, Epidemiology, and End Results (SEER; a population-based registry with 60,089 men) during 2000–2004, the National Cancer Database (NCDB; a hospital-based registry with 63,303 men) during 2004–2005, and the 2,847 men diagnosed with prostate cancer in the PLCO trial between 1993 and 2001.

Results indicated that the patients studied in PIVOT were older and sicker than those found in the general population. The mean age of men at diagnosis in PIVOT was 67.0 years, compared to 65.8, 61.3, and 60.2 years in PLCO, SEER, and NCDB, respectively. Overall mortality in PIVOT was also higher: 64% over 12.7 years, compared to between 8% and 23% in the other databases over a similar timescale (7.5–12.3 years). "Our work shows that the PIVOT trial used a sample of patients who were not representative of the real population affected by prostate cancer," explained Dr Firas Abdollah, Henry Ford Hosptial.

"Our work shows that the PIVOT trial used a sample of patients who were not representative of the real population affected by prostate cancer..."

These results challenge the relevance of PIVOT and suggest that further studies are required before the relative benefits of intervention versus observation for prostate cancer can be properly defined. As Dr Abdollah summarised: "The direct clinical implication of the PIVOT study is that we should abandon surgery in virtually all prostate cancer patients and limit our management to observation. However, in most experts' opinion, this would result in a significant increase in the number of men with metastatic prostate cancer, and in those who will succumb to the disease."

Prostate Magnetic Resonance Imaging Reduces the Need for Invasive Prostate Biopsies

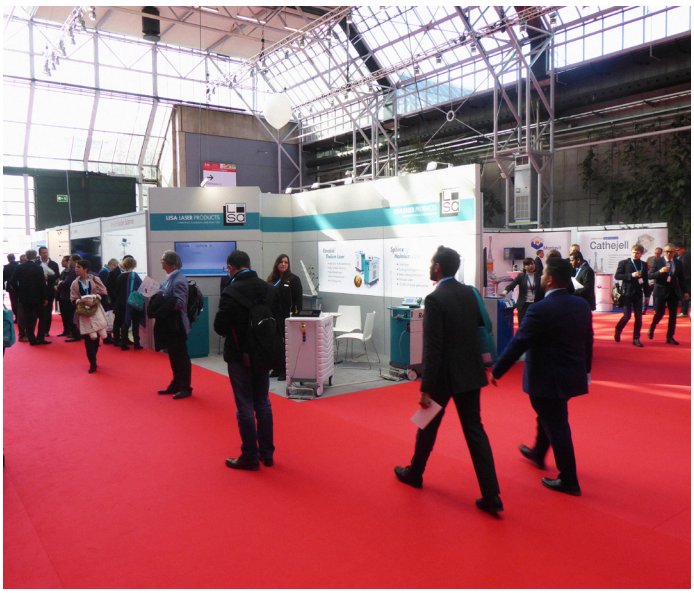
MAGNETIC RESONANCE IMAGING (MRI) scanning during prostate cancer diagnosis can be used to identify harmful prostate cancers that require treatment, preventing overdiagnosis. The PRECISION trial is the first international, multicentre, randomised trial to show such benefits of MRI in prostate cancer diagnosis, and the results were detailed in a EAU press release dated 19th March 2018.

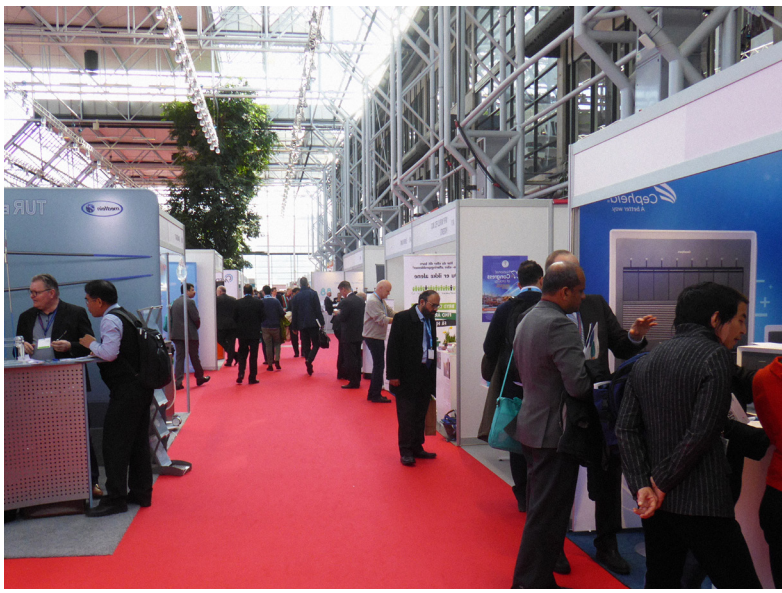
With the aims of reducing the need for biopsy in patients with clinically insignificant disease and providing better diagnostic information than traditional transrectal ultrasound-guided prostate biopsy (TRUS), which can often miss tumours during the procedure, the PRECISION trial investigators performed MRI scans on suspected prostate cancer cases. A total of 500 men were allocated to have either a 10–12 core TRUS biopsy (n=248) or an initial MRI scan and then a biopsy only if an abnormality was found (n=252).

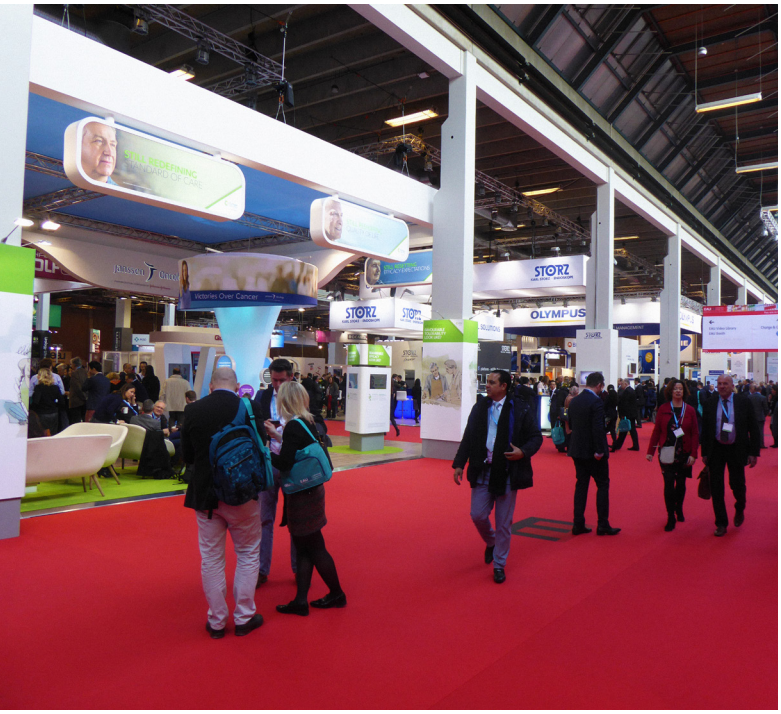
The team noted that clinically significant cancer (Gleason score ≥3+4) was detected in 38% of men in the MRI and biopsy group versus 26% of men who received only the TRUS biopsy, equating to an absolute difference of 11.7% after adjusting for centre effects (p=0.005). In addition, after initial scanning 28% of men in the MRI group were shown not to require a biopsy at all. "This shows that a diagnostic pathway with initial MRI assessment followed by biopsy when required, can not only reduce the overall number of biopsies performed, but can give more accurate results than TRUS biopsy alone," commented Dr Veeru Kasivisvanathan, University College London, London, UK. The team also found that patients who had initial MRI screening experienced fewer side effects because the specific cancerous area was identified, meaning fewer biopsy cores were required.

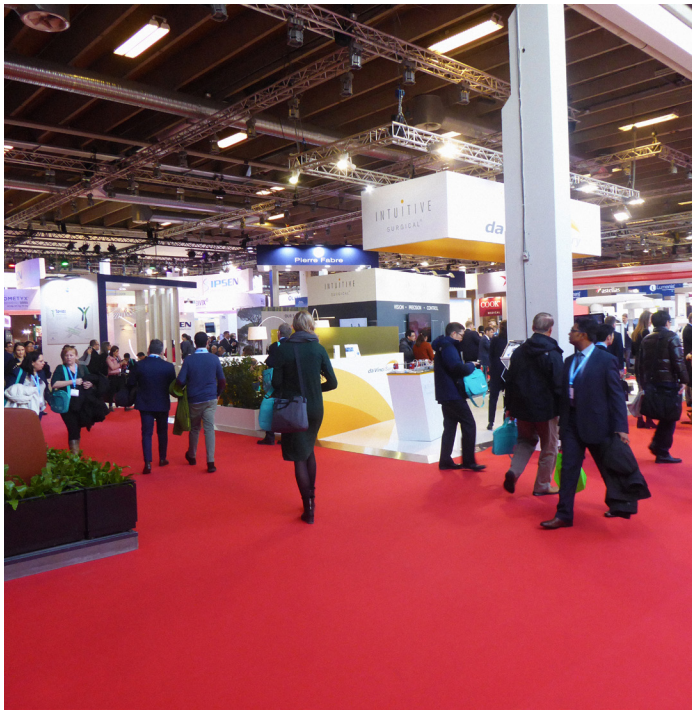
For MRI to be considered part of the diagnostic process in prostate cancer, the researchers described the need for appropriate clinician training and an increased capacity to perform the screening. However, the significance of the results was reinforced by Prof Hein van Poppel, EAU Adjunct Secretary General, University Hospitals of the Leuven, Leuven, Belgium, who stated: "This work shows that using MRI to decide whether or not to perform biopsy has the potential to save around a quarter of a million European men each year from going through the biopsy procedure, and so may be cost-effective in the long run."

"This work shows that using MRI to decide whether or not to perform biopsy has the potential to save around a quarter of a million European men each year from going through the biopsy procedure..."









Prostate Cancer Diagnosis via Artificial Intelligence

ARTIFICAL INTELLIGENCE has been shown to have a promising future in the diagnosis of prostate cancer, according to the results of a study reported in a EAU press release dated 16th March 2018. The researchers suggested that they have developed the first machine-based analysis system that can accurately diagnose prostate cancer. As prostate cancer is the most common cancer diagnosed in men globally, with approximately 1.1 million annual diagnoses, improvements to the diagnostic process are critical to improve patient outcomes.

"In the short term, this can offer a faster throughput, plus a greater consistency in cancer diagnosis from pathologist to pathologist, hospital to hospital, country to country."

The Chinese research team developed an analysis system that utilised machine learning. The system was 'trained' using 918 prostate whole mount pathology section samples obtained from 283 patients using robot-assisted laparoscopic radical prostatectomy. The 918 images were divided into 40,000 smaller samples, of which 30,000 were used to train the software via machine learning. To determine the accuracy of the system, the diagnosis made by a human pathologist was treated as the gold standard to which the system's results for the remaining 10,000 samples were compared. This comparison found the system was able to make an accurate diagnosis in 99.38% of cases.

Furthermore, it appeared that the system was also able to accurately classify the malignancy of the cancer; initial comparisons have found that the system and a human pathologist attributed the samples with similar Gleason scores. However, the authors noted that their sample contained more Gleason score 3 and 4 compared to other grades and that this might have influenced the machine learning process. Researchers are considering suitably objective standards to enable validation of the system's Gleason score analysis to further test and improve the software.

While discussing the future impact of this development in artificial intelligence, the study leader, Dr Hongqian Guo, Nanjing Drum Tower Hospital, Department of Urology, Nanjing, China, explained that an experienced human pathologist would be required to bear responsibility for the ultimate diagnosis, but concluded: "In the short term, this can offer a faster throughput, plus a greater consistency in cancer diagnosis from pathologist to pathologist, hospital to hospital, country to country."

Quality of Life Results for Partners of Prostate Cancer Patients

Results from one of the first studies investigating how prostate cancer affects the partners of patients were presented in a EAU press release dated 19th March 2018. The results of this study indicated that role change, isolation, and the fear of losing a loved one were three key factors affecting the quality of life (QoL) of partners of prostate cancer patients.

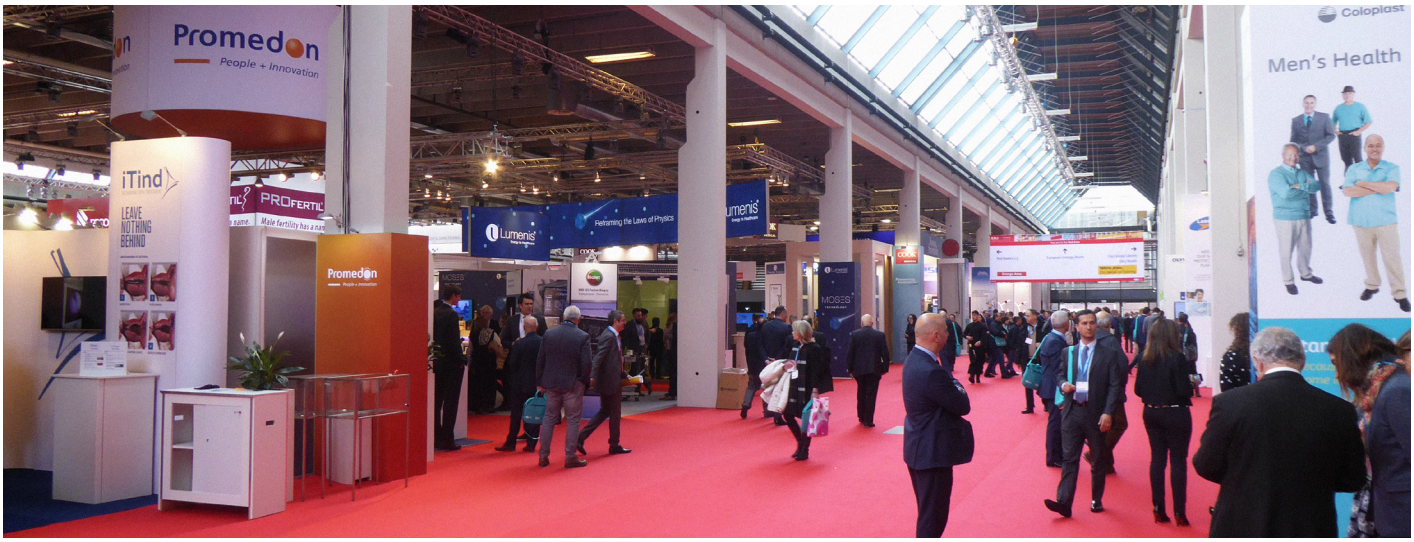
To investigate the factors that affected the QoL of patients' spouses and to identify how healthcare professionals can help reduce these burdens, a total of 56 women were questioned on how their partner's cancer affected their lives. The study, led by registered nurse Ms Jeanne Avlastenok and Dr Peter Østergren, Herlev and Gentofte University Hospital, Herlev, Denmark, showed that nearly half (46%) of the 56 women reported that their partner's health had impacted their own health.

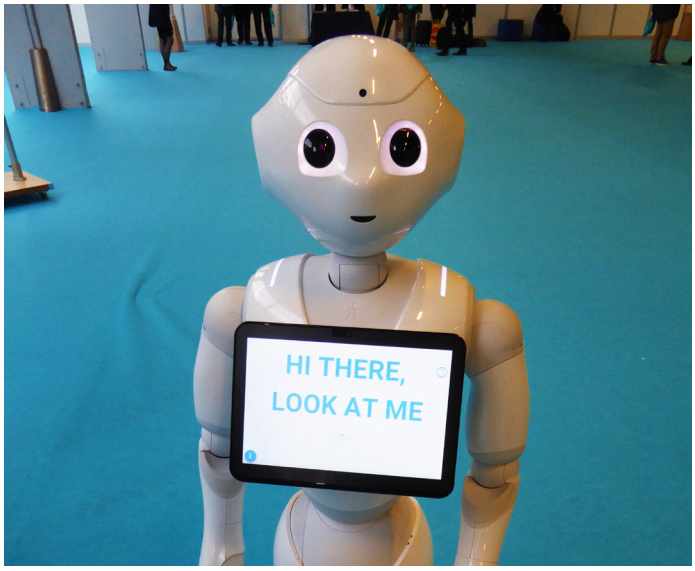
Of the 56 women, 8 were randomly selected for further, in-depth, focussed-style interviews to ascertain how each woman was being affected by their partner's illness. Ms Avlastenok explained: "We worked with the women as a group, encouraging them to be open about what they felt in a supportive, group environment." She went on to elaborate: "Many felt increasingly socially isolated. Their husbands were fatigued both by the illness and by the treatment, which meant that they couldn't socialise as a couple, which made the women feel cut off from social support."

Many studies investigating how prostate cancer affects QoL focus on the impact on the patient, and the partner's QoL is often overlooked and neglected. Results from the study highlighted three specific areas that spouses identified as key factors affecting their QoL: role change, isolation, and the fear of losing a loved one. Identifying these factors allowed the spouses to pinpoint tools that they would find helpful, including written materials on how to deal with emotional issues, what the expected disease course is, and how to prepare for losing a loved one. This study has allowed a better understanding of the effect advanced prostate cancer can have on a spouse's QoL, hopefully allowing spouses of prostate cancer patients to feel more supported in the future.

The team highlighted that the focus group findings were very much qualitative work in a small sample population, but also emphasised why this study was so critical in the journey to better support relatives of seriously ill patients. Dr Østergren commented: "[...] In any study, you need to do the qualitative work before moving to any larger sample. We need to let the women express their concerns first, so we can understand which questions to ask."

"We need to let the women express their concerns first, so we can understand which questions to ask."





The Role of Patients in Decision-Making for Prostate Cancer Treatment

ENSURING patients with prostate cancer take part in the decision-making process during their treatment was recommended by researchers at the EAU Congress as a result of a recent study. This study was presented as part of the 'EAU Nurses Thematic Session 5: Shared decision-making: Putting patients at the heart of urology care' on 17th March 2018.

Currently, there is scientific debate about the right course of action to take as a medical professional when a patient asks you to make the treatment decision for them. There are two potential courses: suggest a treatment option for the patient in order to allow the patient to play the decision-making role they prefer, or encourage the patient to be actively engaged in the decision about their treatment. There have been studies that support both options. Therefore, the researchers conducted a prospective, multicentre, observational study to determine which course of action was most appropriate for patients with localised prostate cancer.

Around 450 patients were involved in the study. Before the patients were treated, researchers asked them several questions about their preferred level of involvement in decision-making. Answers showed that 89% of patients expressed the desire to be actively involved in the decision-making process (n=403). Three months after the patients had undergone treatment, the researchers questioned them to find out whether they had been included in decision-making. Overall, 87% of patients reported active involvement, with 83% of patients experiencing their preferred decision-making involvement.

It was found that there was an association between active involvement in decision-making and less decisional conflict (Cohen's *d* [effect size]: 0.52), less decisional regret (Cohen's *d*: 0.34), and greater knowledge of prostate cancer (Cohen's *d*: 0.30). Furthermore, a significant association was not found between role concordance and decisional regret or knowledge of prostate cancer. Lead study author, Dr Marie-Anne van Stam, Department of Urology, The Netherlands Cancer Institute, Amsterdam, Netherlands, stated: "These findings indicate that patients with localised prostate cancer who indicated that they had been actively involved in treatment decision-making were better informed about their cancer and its treatment, experienced less uncertainty about the treatment decision, and had less regret about the chosen treatment, compared to patients who reported having experienced passive involvement."

"...patients with localised prostate cancer who indicated that they had been actively involved in treatment decision-making were better informed about their cancer and its treatment..."

Giving Urology Patients a Voice

PATIENT INVOLVEMENT was a key theme across many abstracts, symposia, and campaigns presented at this year's EAU Congress, with the overall aim of assessing the current unmet needs and improving quality of life for patients with urological conditions.

The EAU patient information (EAU PI) working group writes and disseminates guideline-based non-biased information on different urological conditions, allowing patients to inform themselves and become more involved in the management of their conditions. Dr Giulio Patruno, Policlinico Tor Vergata Roma, Rome, Italy, explained how the EAU plays a pivotal role in delivering a universal message to increase awareness of urological conditions, particularly to a shy male population with conditions that are not often discussed publicly.

"We are asking the European Union (EU) to help sustain awareness regarding prostate cancer, provide the means to improve both diagnosis and treatment, and support equity of management for all."

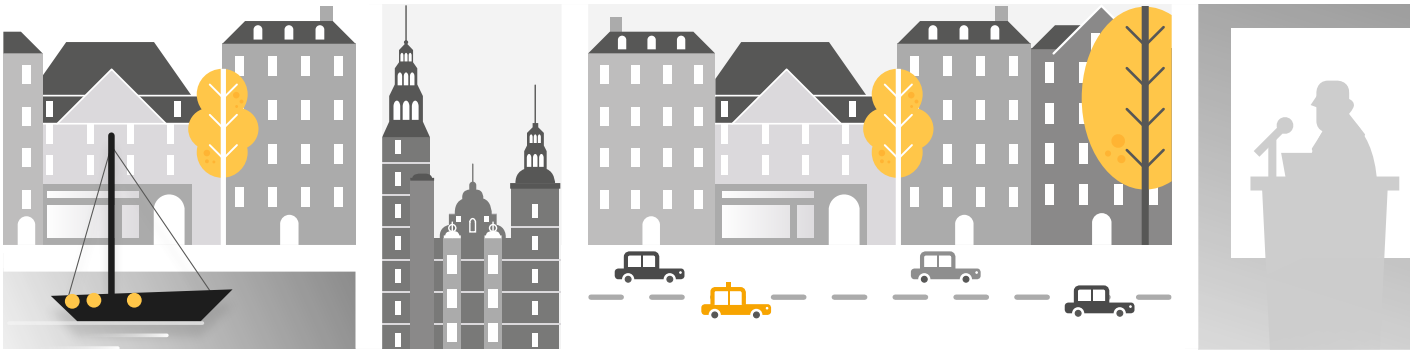
During one abstract presentation at the 2018 EAU Congress, results were reported that showed urological cancer patients had a 5-times higher risk of committing suicide than people without cancer; this emphasised the need for quality of life evaluation. For example, Dr Sarah Ottenhof, Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands, described how the field of penile cancer research now uses patient-reported outcome measures in the clinic and pre and postoperatively to measure subjective factors in men. In addition, in a EAU PI session on prostate cancer, Mr Ken Mastris, Chairman of Europa Uomo, stated: "We are asking the European Union (EU) to help sustain awareness regarding prostate cancer, provide the means to improve both diagnosis and treatment, and support equity of management for all."

Looking to the future, when asked how the impact of patient information can be increased, Dr Patruno stressed the importance of using social media and the power of hashtags to increase awareness at a European level as well as worldwide. In addition, Dr Ottenhof explained that the EAU must continue to work together with patient advocacy groups to discuss patient experiences and investigate patients' needs and what is important to them.

Animated Videos Improve Patient Understanding of Surgical Procedures

The EAU patient information (EAU PI) working group has demonstrated the positive effect animated videos of surgical procedures have on patients' understanding of their forthcoming procedure, according to information presented at the 2018 EAU Congress.

Rising from EAU's mission to improve the level or urology care, the EAU PI was created as a collaborative European body for the benefit of patients and their families, equipping them with information to talk about the issues that worry them the most and encouraging meaningful dialogue between patients and their physicians. EAU PI aims to provide reliable, clear, and unbiased information, and, as a result, is constantly in search of new methods to improve patient understanding of their treatment.



Following the Winter et al.[1] study and its positive response regarding portable video media improving patient knowledge and satisfaction, the EAU PI launched its own pilot study. The EAU PI developed an animated video explaining urological treatments in a clear and comprehensive manner.

To conduct the study, a video explaining ureteroscopy was shown, alongside written information, to patients about to undergo the procedure before they had any contact with hospital staff. After the patients had watched the video and read the written information, they were presented with an 11-item questionnaire for them to rate their experience followed by two extra questions to assess their understanding of the information.

Questionnaires were collected from three countries around the globe: Germany (n=52), Turkey (n=51), and China (n=17). Participants had an age range of 19–>59 years. Positive satisfaction comments were received from 90% of responders, and 99% of responders considered the information favourable for preparing them for the procedure; <2% found the information unfavourable. Analysis also identified areas requiring further clarification for patients to more completely understand their forthcoming procedure.

The results from this pilot study confirmed that the patients' level of understanding of their surgical procedure and their confidence before the procedure were enhanced and improved by the use of a cartoon animation. The researchers did emphasise that this method is not intended to replace face-to-face interaction and discussion with a physician but should be used in parallel, providing an extra level of information.

EAU PI have prepared further animated videos on topics including drug treatment of overactive bladder, placement of JJ stents, and percutaneous nephrolithotomy, with even more planned for the coming year.

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Call for Adherence to Guidelines in Penile Cancer

ADHERENCE to EAU guidelines has been found to dramatically improve survival rates in patients with penile cancer. These findings were reported in a EAU press release dated 16th March 2018. Indeed, patients who did not receive the gold-standard treatment, as recommended by the guidelines, had approximately half the survival rate compared to those who did.

Researchers conducted a retrospective analysis of 425 patients from 12 centres from across the globe who had been treated for penile cancer between 2010 and 2016. The surgical approach that should have been taken according to the 2016 EAU guidelines was compared to the

"From our work, we see that around twice as many patients survive if they have been treated according to recommended guidelines."

surgical approach that was carried out for the primary surgery and the lymphadenectomy. Several analyses were conducted to calculate the influence of adherence to the guidelines on survival: descriptive, univariate, and multivariate analyses; researchers also estimated Kaplan–Meier curves.

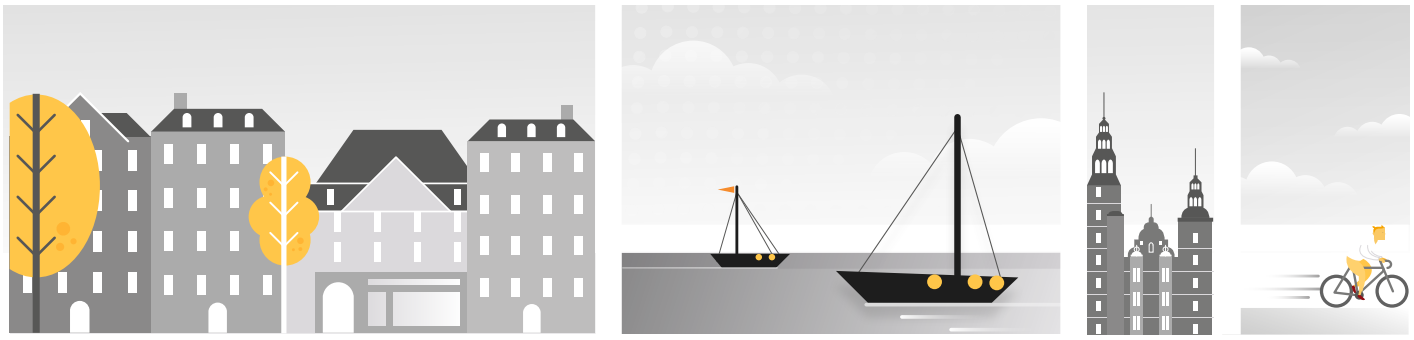
The study's primary author, Dr Luca Cindolo, Department of Urology, ASL Abruzzo, Chieti, Italy, discussed the results, stating: "We found that most patients were treated in accordance with the gold-standard EAU recommendations, but around 25% of patients had not received appropriate treatment. From our work, we see that around twice as many patients survive if they have been treated according to recommended guidelines."

The study also investigated why patients were not treated according to guidelines; 17% of the time this was due to the patient's choice and over half was due to the surgeon's choice (52%). Other causes accounted for 31% of cases of non-adherence to guidelines. Understanding why non-adherence occurs should help facilitate greater application of the guidelines. One suggested solution was provided by Dr Vijay Sangar, Director of Surgery, Christie Hospital, Manchester, UK. Dr Sanger explained: "We can suggest that if we treat rare cancers in national or even international centres of excellence, the chances of better management improve."

A Brief History of Urology

With its focus on education and the very latest innovations, the 33rd Annual EAU Congress is nothing if not progressive. That is not to say, however, that it has forgotten the past. On the contrary, this year's EAU Congress showcased the association's history as never before, with the EAU History Office celebrating not only the urological history of Denmark, but that of the whole of Scandinavia. On the 100-year anniversary of the end of World War I, we also take this opportunity to reflect on wartime urology and how the Great War shaped this discipline as we now know it.

The study of urology is ancient in origin, spanning a variety of cultures including Babylonian, Egyptian, Indian, and of course, Ancient Greek. Indeed, the term 'urology' is derived from the Ancient Greek 'οὖρον' (ouron, 'urine') and '-λογία' (-logia, 'study of'); thus, it comes as no surprise that the colour and sedimentary quality of the urine were of great concern to early physicians. It is easy to dismiss this formative period of urology as primitive, but, in reality, it was far from it; writings from Hippocrates, Erasistratus, and Galen, among others, describe the accurate diagnosis of a variety of conditions within the urinary system and the use of a variety of tools and procedures, including catheters and lithotomy.



Urology continued to grow in importance throughout the middle ages, featuring prominently in the writings of major physicians, such as the famous polymath Avicenna (also known as Ibn Sīnā). Analysis of urine continued to dominate during this period, with artwork from the period frequently displaying a physician examining a glass of urine.

Urological study, like so many fields of medicine, blossomed throughout the Renaissance, though the focus ultimately remained on urinary analysis. This changed dramatically in 1879, when Joseph Leiter and Maximilian Nitze first publicly demonstrated their revolutionary invention: the Nitze–Leiter cystoscope. The advent of this device meant the ability to visually examine the urinary system without surgery for the first time and led to urology's rapid evolution into the speciality we know today.

Urology in World War I

On the centennial anniversary of the end of World War I, the EAU Congress paid homage to the physicians of the conflict, many of whom went on to become influential urologists, including Roger Ogier Ward (1886–1971) who served as a distinguished artillery officer and was later the driving force behind, and first president of, the British Association of Urological Surgeons (BAUS). A co-founder of the BAUS, Victor Wilkinson Dix (1899–1992) served in the Royal Flying Corps and would also become president of the BAUS in 1962. Sir Eric Riches (1897–1987) is another famous name and yet another president of the BAUS (1951). Well known for developing the Riches cystoscope in 1955, which remained popular until the introduction of the Hopkin's rod lens system; his obituary in the British Journal of Urology describes him as "a Giant among Giants" in the field of urology.

War has often been a catalyst for medical progress, and those who experienced such times often made extraordinary contributions to the medical fields. This year, the EAU remembered the past and celebrated the incredible advances made during peacetime.

Urology in Scandinavia

Being held in Copenhagen, the EAU took this opportunity to explore the rich history of not only Danish urology, but that of Scandinavia as a whole. Internationally recognised names include Sven Ivar Seldinger (1921–1998), whose guidewire technique is still used daily; Jan-Erik Johansson (b. 1946), hugely influential in the noninterventional management of prostate cancer; and Tage Hald (1934–2004), whose revolutionary visual depiction of lower urinary tract symptoms we now know as 'Hald's rings' were celebrated.

The countries of Scandinavia share a plethora of cultural and linguistic ties, facilitating an ever-growing camaraderie in the field of urology. In 1950, the friendship of the Danish Olav Povlson and the Swedish Gustav Giertz led to the creation of a urology travelling club; in 1956, this club became the Scandinavian Association of Urology (NUF), which, to this day, champions collaboration between Denmark, Norway, Sweden, Finland, and Iceland.

"...EAU Congress provided a urological experience par excellence, with countless opportunities to network, learn, and share ideas."

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Interviews

Presenting a collection of interviews from our Editorial Board members

Featuring: Dr Roberto Sanseverino and Prof Roger Dmochowski

Dr Roberto Sanseverino

ASL Salerno, Italy

The EMJ team interviewed Dr Sanseverino at the European Association of Urology (EAU) Congress 2018 in Copenhagen, Denmark. What follows is a transcription of that interview.

What inspired you to focus your career on urological disorders?

It is mainly a familial story because my father was a urologist too. I think that urology is quite a complete speciality, with surgical disciplines and also a very big medical part, so it is really amazing for me to be involved in the urological field. So, it is both family history as well as personal interest.

What is your favourite aspect of your job?

In general, it is very interesting to deal with patients, as in any medical speciality, and it is interesting to cover so many different topics in urology. The field goes from surgical oncology to medical therapy in andrology or endocrinology, so it is a very wide and complete speciality that is really fascinating. Of course, in the modern era it is difficult to cover all areas of the field, but it is one of the challenging aspects of our discipline.

From your perspective, what have been the most important advances in urological surgery recently, and what impact has that had on the clinical setting?

I think the main development in urology is minimally invasive surgery, which has been popular in urology for a long time. Urologists are pioneering endoscopy of the bladder and of the upper urinary tract, and are now working towards the evolution of laparoscopy and robotics. Even in the diagnostic and therapeutic sectors, it is different from other disciplines like gastroenterology and general surgery in which,

in the diagnostic setting, the gastroenterologist is now completely separate from surgery; the urologists have been smart enough to keep everything within the scope of their role. So, I think that the evolution toward minimally invasive surgery in general is one of the most exciting aspects of our discipline.

How important do you feel the co-operation is between urologists and other medical professionals from other disciplines, for example oncologists, with regard to patient wellbeing? What do you think can be done to strengthen the relationship between the different disciplines?

This is very important, in my personal opinion, and it is also the general consensus in the field. I am part of the board of directors of the Italian Society of Uro-Oncology (SIUrO), and we are working a lot in this direction because teamwork has been shown to be very effective, especially in the quality of treatment and satisfaction of patients; so, it is really a direction to go in. There are of course some countries that are far ahead in comparison to where I work and live in Italy. For example, in Germany, prostate cancer units are already very well established. It is also a problem to make the directors of the hospital and all of the regulatory system staff understand that teamwork is not something that should be separate from the normal work, it should be part of the everyday practice in the field of oncology, but it is now emerging in other sectors. For example, in the treatment of urolithiasis there is now a tendency toward teamwork with nephrologists and with specialists of metabolism. It is a new concept of modern medicine where the amount of knowledge is so big that it is impossible for only one person and one specialist to cover all the knowledge in any specific discipline. I think it is really the new revolution; the problem is that it is sometimes difficult to make specialists work together and to make them understand that teamwork should be the future.

"I think the main development in urology is minimally invasive surgery..."

"It was not possible before, but now you can have your own personal roadmap through the congress. It is very important not to listen to everything but to choose a sector and to follow the line of the argument throughout the congress."

What is the most exciting thing you have seen at this year's EAU congress so far?

I have found that this year's congress has been a really huge event and it is getting better and better year by year. I am also a member of the American Urological Association (AUA), so I can compare the two situations; several years ago there was such a big difference. The AUA was so much better from a scientific point of view, in terms of organisation, and so on. Now the EAU is closing the gap and it is becoming a bigger and bigger congress, with significant improvements from a scientific and organisational point of view. We must remember that urology was born in Europe and many of the milestone innovations in our field came from Europe.

Why do you feel that congresses like this one are so important for young urologists to attend?

It can be a little difficult to manage such a big convention, but it is a wonderful opportunity because in the same congress you can have many kinds of educational programmes. I think that even for a young urologist, it is a tremendous opportunity to see the top leaders in a specific field doing something or talking about something. So, I think it is still very important for young specialists to attend these big congresses.

What would your advice be for someone attending a congress like this one for the first time?

It was not possible before, but now you can have your own personal roadmap through the congress. It is very important not to listen to everything but to choose a sector and to

follow the line of the argument throughout the congress. Many innovations are presented during these big meetings, and that's why in our national congresses we now try to make an update session of these big congresses, such as AUA, American Society of Clinical Oncology: Genitourinary Cancers Symposium (ASCO-GU), or EAU, just to make this information available for as many people as possible. Not many people can afford to come and visit the EAU or even less the AUA, and it is getting more difficult to have the opportunities to attend these congresses. So, it is important to get a real feeling of the congress and to transmit this to other people.

"...it is getting more difficult to have the opportunities to attend these congresses. So, it is important to get a real feeling of the congress and to transmit this to other people."

Prof Roger Dmochowski @LinkedIn

Vanderbilt University Medical Center, USA

Firstly, what inspired you to focus your career towards urological disorders?

I was inspired by a senior urologist who took an earnest interest in my career and supported me as a unique person. His recognition of my personal goals and interests was a profoundly gratifying experience. This experience exemplified for me the significance of mentorship and the importance of the departing generation engaging and caring for the incoming one.

Who was the most influential person during your training as a urologist and why?

There were two people who were profoundly influential during my training. One was a senior faculty member and the other was a senior registrar who acted as a supporter for my interests and, due to his experience with the training programme, provided his personal experience and knowledge for navigating the training process.

"I was inspired by a senior urologist who took an earnest interest in my career and supported me as a unique person."

You are a member of a significant number of societies, deliver key guest lectures, and feature in many training protocols; beyond this, you have published >230 papers and presented >340 abstracts, but what is your favourite aspect of your job?

My favourite aspect of my job is mentoring the next generation and providing life insights into the vicissitudes of the physician's existence and medical training. The times are difficult for the next generation, as altruism seems lost in medical economics and governmental controls.

You have been a medical professional since 1983. During your 35 years in the hospital setting, what is the most fascinating case you have worked on?

Each case is different and impacted by the individual who suffers the malady for which they seek redress. I cannot think of one archetypal individual patient but rather the confluence of experiences with a variety of patients, many of whom have been forsaken by other providers and given no hope for their current circumstance. Perhaps the most substantive message is that each person is unique, each person seeks help, and the act of listening, the attempt to communicate, and the

honest exposition of what is possible is most important to patient engagement.

Antibiotic resistance is an ever-growing concern and an area you have focussed your studies towards. What do you believe is the most important factor in promoting excellent antibiotic stewardship?

Antibiotic stewardship is a cultural and philosophical change for urology; we must become more stringent with antibiotic use, choice, and magnitude of exposure. Also, integral to the control of antibiotic use will be the education of patients, encouraging them to avoid the desire for, and use of, antibiotics for any malady.

From your perspective, what have been the three most important advances in urological surgery and why? What impact have these developments made on clinical settings and patient outcomes?

The three most significant advances have been robotic surgery, improved pain management and pain control, and the trend towards reduced inpatient hospitalisation. All of these have contributed to improved outcomes and (I think) patient satisfaction.

What key topic or issue, in your opinion, should be the focus of the urological community over the next 5 years?

The most significant issue for urology is the age of the current cohort of urology specialists and manpower constraints for the future care of patients. With an ageing population, a reduced number of specialists will provide substantive stress to the quality of care.

You have made great efforts towards analysing infection rates in urology patients. What are the implications that your studies have for the wider medical community?

The major finding from our study is the need to reduce antibiotic use, and that antibiotics are chosen to decrease temporal exposure. Indeed, symptoms do not indicate the need for antibiotics for the majority of patients.

Statistics have long suggested that uptake of medical treatment and support is significantly lower in men than women. Is this something that you see when working in the clinic? What do you think can be done to improve male engagement in their health and medical treatment?

Men tend to seek medical treatment less frequently and often delay seeking healthcare for symptoms and conditions. This trend is gradually changing as women become more forceful in relationships, and as urologic conditions as well as general medical conditions become more demystified.

Finally, why do you think congresses are so important to the medical community? What advice would you give to someone attending congress for the first time?

Congresses are critical to support collegiality and the interchange of ideas. When attending a conference for the first time, make one or two strong acquaintances that will hopefully last for a lifetime.

"Antibiotic stewardship is a cultural and philosophical change for urology; we must become more stringent with antibiotic use, choice, and magnitude of exposure."

VIEW MORE INTERVIEWS ONLINE ←

Abstract Reviews

This year's wide selection of reviews come straight from the 2018 EAU Congress, and have been hand-picked by our Editorial team

A Novel, Non-Invasive Aid for Bladder Cancer Diagnosis: A Prospective, Multicentre Study to Evaluate the ADXBLADDER Test

Authors: *Stuart McCracken

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Disclosure: The author is a paid consultant of Arquer Diagnostics.

Keywords: Biomarker, bladder, cancer, diagnostic, enzyme-linked immunosorbent assay (ELISA), haematuria, urine test.

Citation: EMJ Urol. 2018;6[1]:32-33. Abstract Review No. AR1.

This poster presentation, which was named Best Poster in Session, was presented at the European Association of Urology (EAU) meeting in Copenhagen, Denmark on Monday 19th March 2018 in the context of a number of discussions throughout the conference regarding the utility of biomarkers as an aid to or replacement for cystoscopy in some patient types.

EAU guidelines state that cystoscopy represents an important step in the diagnosis and management of bladder cancer. However, poor visualisation caused by inflammatory conditions or bleeding, and/or the presence of flat urothelial lesions, can lead to up to 30% of tumours being missed. Cytology is often used as an aid to cystoscopy but, given that cytology sensitivity for low grade tumours is very poor, there is an unmet need for a nonsubjective method of detecting the presence of cancer. Urinary biomarker tests are a good candidate method for overcoming these issues. While numerous urine markers have been developed, none have been recommended for primary detection of bladder cancer to date, despite evidence suggesting that cystoscopy detection rates for urothelial carcinoma were significantly higher in cases where urologists were aware of a positive urine test result, compared to when they were not ($p<0.001$).[1]

This poster presentation summarised a performance evaluation of the use of ADXBLADDER, a new, simple, and rapid sandwich enzyme-linked immunosorbent assay (ELISA) test, for its use in the diagnosis of bladder cancer. ADXBLADDER is based on the biological principle that in order for cells to

divide they must replicate their DNA accurately. This requires regulation, involving the DNA licensing system of which the MCM5 protein is a key member. Usually, MCM5-positive cells are confined to the basal stem cell compartment of the bladder and are not seen at the surface of the epithelium. In cancer, differentiation is arrested; MCM5-positive cells are found at the surface of the epithelium where they are exfoliated into the urine and can be measured with the ADXBLADDER test. The objective of this study was to evaluate the performance of ADXBLADDER in the diagnosis of bladder cancer.

The study was a multicentric trial carried out at six UK sites. Full void urine samples were collected from patients attending the urology clinic with haematuria (both microscopic and macroscopic). The ADXBLADDER test was performed on the collected urine and the results compared with those of the standard haematuria pathway investigations.

In total, 577 patients were included in the study, with an 8% prevalence of bladder cancer. The overall sensitivity and specificity were 76% and 69%, respectively, which contributed to a negative predictive value of 97%. On closer examination, the combined sensitivity of the muscle invasive and high risk non-muscle invasive bladder cancers was found to be 95%. A subset analysis of the available cytology data compared to ADXBLADDER (consisting of 10 bladder cancer patients) showed positivity in 2 out of 10 samples for cytology and 8 out of 10 for ADXBLADDER.

The study concluded that ADXBLADDER is a simple, rapid, and reliable test and showed that the ADXBLADDER test can be used in the detection of bladder cancer and could replace urine cytology.

The discussion following the presentation of this study centred around the observation that the previous biomarkers available, such as NMP22, were affected by visible haematuria, inflammation, and infection; however, as ADXBLADDER detects a marker of proliferating cells, it is unaffected by these conditions.

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Gel Casting as an Approach for Tissue Engineering of Multilayered Tubular Structures: Application for Urethral Reconstruction

Authors: Melissa van Velthoven,[1] Rana Ramadan,[1] Barbara J. Klotz,[2] Debby Gawlitta,[2] Pedro F. Costa,[3,4] Miguel D. Castilho,[3] Jos Malda,[3,5] Laetitia de Kort,[1] *Petra de Graaf[1]

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Corpus spongiosum (CS), hydrogel, tissue engineering, urethra, urology.

Citation: EMJ Urol. 2018;6[1]:33-35. Abstract Review No. AR2.

Currently, there is a lack of tissue-engineered solutions for replacement of urological tissues, like ureters and the urethra and corpus spongiosum (CS). The bottlenecks to these solutions are vascularisation and the complex tubular organisation composed of different cell layers. The CS is an integral part of the urethra and is important in supporting its function. In cases of a healthy CS, success rates of replacement with epithelial tissue, like oral mucosa, can reach up to 90%. However, in cases of severe fibrosis or the absence of CS in congenital disease (hypospadias), tissue engineering of the urethra should be combined with reconstruction of the CS.[1] In a series of presentations at European Association of Urology (EAU) Congress 2018, the use of tissue-engineered oral mucosa grafts (TEOMG) for urethral reconstruction was discussed. In one study, TEOMG reduced the rate of donor morbidity and was successful in around 67% of cases.[2] Success rates were dependent on the number of prior surgeries: the more prior surgeries the higher the risk of recurrence of stricture. In cases of failure, the CS may be affected by severe fibrosis due to previous intervention and these patients may benefit from our innovative casting approach to engineer a three-layered tubular construct to mimic the organisation of the native CS.

As part of our poster (poster 285), we presented the CS as a multilayered, highly vascularised structure with distinct distribution of extracellular matrix components (Figure 1A). A mould with three chambers, representing the three layers of the CS, was designed and fabricated. The chambers were loaded with gelatine-based hydrogels containing a coculture of endothelial cells and pericytes (chambers 1 and 3) and smooth muscle cells (chamber 2) (Figure 1B). A fibre mesh was placed at the base of the construct to serve as a porous support for the gels and to roll the construct into a multilayered tubular construct. The gels were mechanically tested and compared to native CS and could easily be rolled into multilayered tubular constructs.

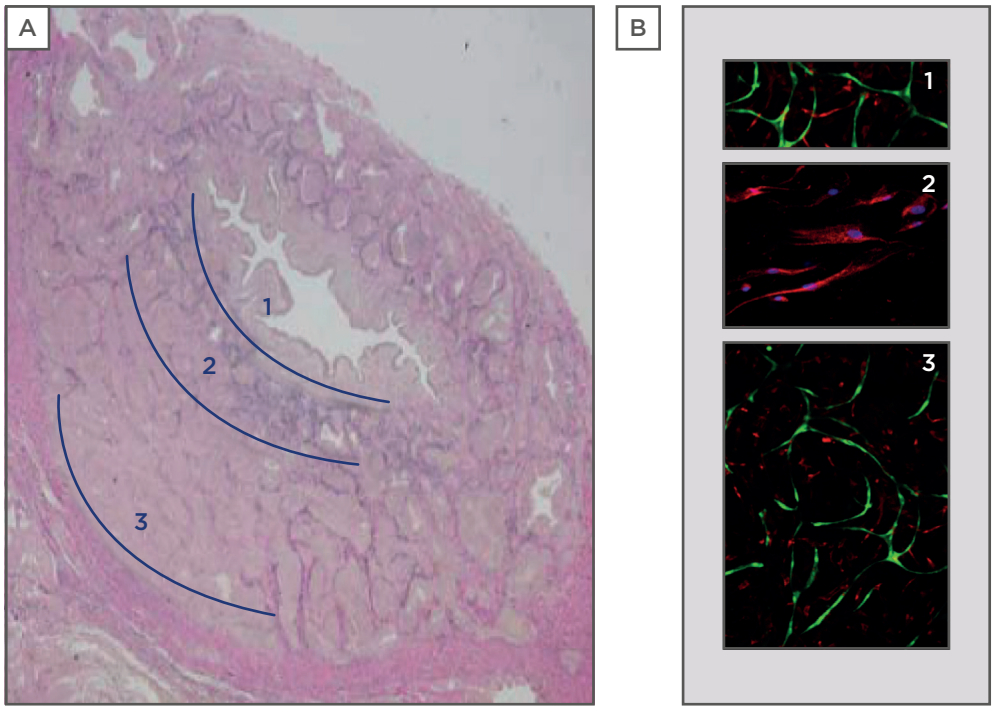

Figure 1: Engineering of a multilayered graft.

A) The three layers of the human corpus spongiosum can be distinguished: 1) rich in microvessels; 2) elastin-rich; and 3) rich in vascular spaces and microvessels (3 µm tissue section, elastin staining in purple). B) Representation of the mould with three chambers, chambers 1 and 3 with endothelial cells (green) and pericytes (red), and chamber 2 with smooth muscle cells (nuclei in blue, elastin staining in red).

The encapsulated cells formed small capillary-like structures (chambers 1 and 3) and produced elastin (chamber 2) within 2 weeks of culturing. The compressive modulus of the construct was comparable to that of the native tissue.

In conclusion, our approach enables construction of tubular structures with distinct composition in the different cell layers. Cell survival and functionality of up to 14 days was achieved. Our next steps will involve upscaling to clinically relevant sample sizes and in parallel testing in laboratory animals to assess whether the vascular networks produced in the hydrogel will adapt to the native vasculature. Our tissue-engineered CS can be combined with future applications of TEOMG, and this approach towards tissue engineering of multilayered tubular structures may be applicable to the urological field, as well as in other fields of soft tissue engineering.

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A Prospective Analysis Concerning the Microbial Resistance Rates in Patients Undergoing Transurethral Resection of the Prostate

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Keywords: Antibiotics, bacteriuria, microbial resistance, transurethral resection of the prostate (TURP).

Citation: EMJ Urol. 2018;6[1]:35-36. Abstract Review No. AR3.

INTRODUCTION AND OBJECTIVES

Fluoroquinolones are the most frequently used antibiotics in transurethral resection of the prostate (TURP) prophylaxis in Belgium, and microbial resistance is an increasing problem in healthcare.[1-3] We aimed to prospectively investigate microbial resistance in our centre to explore the resistance to fluoroquinolones and optimise antibiotic prophylaxis in TURP.

MATERIALS AND METHODS

After ethical committee approval, 506 consecutive patients undergoing TURP between August 2008 and September 2015 were prospectively investigated. A urine analysis (preoperative, at hospital discharge, and 3 weeks postoperative) was performed in addition to an analysis of the blood culture or irrigation fluid and the resected prostatic tissue. Microbial cultures were scored by microbiologists as 0 (not significant), 1 (mildly significant), or 2 (significant). Antibiotic prophylaxis was only used in patients with preoperative bacteriuria or a preoperative indwelling catheter. The majority of antibiotics used were fluoroquinolones (89.5%), followed by amoxicillin (6.0%).

RESULTS

In the patients examined, 42 (8.2%) had significant preoperative bacteriuria. The most common organisms were *Escherichia coli* (28.2%) and *Klebsiella* (21.7%). The preoperative fluoroquinolone-resistance (FQ-R) was 69.2% in *E. coli* and 40.0% in *Klebsiella*. Fifty-eight

patients (11.4%) had significant postoperative bacteriuria at the time of hospital discharge, with *Enterococcus faecalis* the most frequent organism (29.2%), followed by *Klebsiella* (13.2%) and *E. coli* (13%). The postoperative FQ-R was 75% in *E. coli* and 60% in *Klebsiella*.

Three weeks after undergoing TURP, 36 patients (7.1%) had significant postoperative bacteriuria, with *E. faecalis* the most frequent bacteria (44.4%), followed by *E. coli* (36.1%); the FQ-R following TURP was 53.8% in *E. coli.* Thirty-one patients (6.1%) had significant positive blood cultures (at the recovery unit). *E. coli* and haemolytic *Streptococci* were the most frequent organisms (both 19.4%); the FQ-R was 50% in *E. coli*.

Upon arrival at the ward, 24 patients (4.7%) had significant positive irrigation fluid cultures. *E. coli* was the most common organism (29.2%), followed by *E. faecalis* (25.0%); the FQ-R was 85.7% in *E. coli.* Forty-seven patients (9.3%) had a significant positive prostate tissue culture, with *E. faecalis* (36.1%), *Staphylococci* (14.9%), and *E. coli* (12.3%) being the most common organisms present; the FQ-R was 83.3% in E. coli. Finally, 18 patients (3.6%) had uncomplicated fever during or after hospitalisation and 1 patient (0.2%) had septicaemia.

CONCLUSION

A high rate of antibiotic resistance was observed in our patients undergoing TURP, with a remarkable FQ-R in *E. coli*. Our findings could be used to question the use of fluoroquinolones as the most appropriate empiric prophylaxis for TURP patients. We recommend a preoperative urine sample collection a few days before surgery so that a microbial culture-based antibiotic prophylaxis can be utilised in cases of a positive urinary culture.

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The Discrepancy Between European Association of Urology (EAU) Guidelines and Daily Practice in the Evaluation of Nocturia: Results of a Dutch Survey

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Lower urinary tract symptoms (LUTS), nocturia, obstructive sleep apnea.

Citation: EMJ Urol. 2018;6[1]:36-38. Abstract Review No. AR4.

INTRODUCTION AND OBJECTIVES

In addition to the evaluation of voiding symptoms, the medical evaluation (history and diagnostic tests) of patients with nocturia should also consider other related causes, such as sleep disorders, obstructive sleep apnoea (OSA), diabetes, and heart failure. The overall objective

of this survey was to study the discrepancy between the recommendations made in the European Association of Urology (EAU) guidelines on the evaluation of nocturia and the clinical practice of Dutch urologists and urology residents.

MATERIALS AND METHODS

A national cross-sectional survey was sent digitally to 450 urologists and urology residents in the Netherlands. The questions were related to their work setting, field of interest, the number of patients with nocturia, the questions they ask when recording patient history, and the diagnostic adjuncts applied in the evaluation of patients with nocturia.

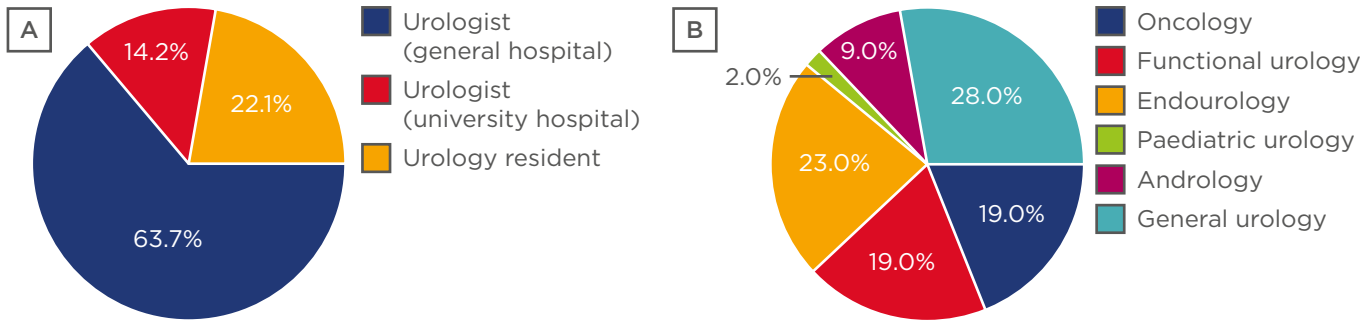

Figure 1: The distribution of Dutch urologists surveyed on the basis of their work setting (A) and their field of interest (B).

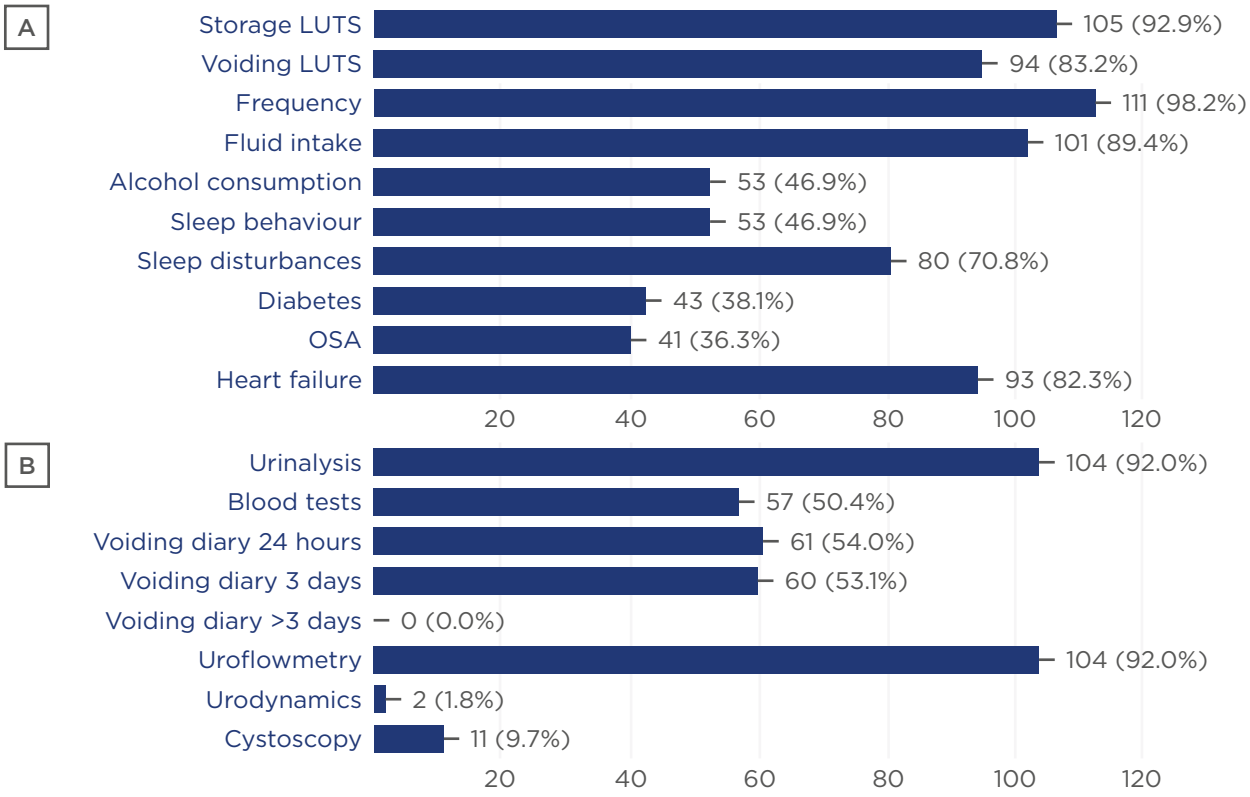

Figure 2: Results of a survey sent to Dutch urologists. The figure shows the percentage of urologists who asked questions about specific topics during patient history (A) and who reported use of diagnostic tests (B).

LUTS: lower urinary tract symptoms; OSA: obstructive sleep apnoea.

RESULTS

A total of 113 questionnaires were eligible for analysis. The distribution of the work setting and field of expertise of the urologists is shown in Figure 1. During history taking, almost all the urologists reported asking patients with nocturia about their storage (93%) and voiding complaints (83%), voiding frequency (98%), fluid intake (89%), and symptoms suggestive of heart failure (82%). However, questions about sleep disturbances (47%) and alcohol consumption (47%) were asked by less than half of the urologists and residents when evaluating nocturia patients. Questions about symptoms suggestive of diabetes (38%) or OSA (36%) were only asked by around one-third of the urologists in this survey. The results of the questions asked during patient history and additional diagnostic test are summarised in Figure 2.

DISCUSSION AND CONCLUSIONS

Although most European urologists claim to apply the EAU guidelines, adherence to them is low in daily practice. This survey shows that only a minority of the Dutch urologists and residents ask about alcohol consumption and symptoms suggestive for diabetes or OSA.

In addition, most of the doctors reported using a bladder diary for either 24 hours or up to 3 days, despite the EAU guidelines grade of recommendation A and level of evidence 2b on the use of a bladder diary for the duration of at least 3 days and up to 7 days.[1]

Regarding the evaluation of patients with nocturia, the results from this study allow the conclusion that the use of a voiding diary for a sufficient length of time (a minimum of 3 days), as well as questions regarding OSA, diabetes, and alcohol consumption, are not applied by the majority of urologists in the Netherlands, which could reflect the clinical practice in other European countries. This observation mandates better education and campaigns to raise awareness on these matters.

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Performance of White Light Imaging Compared to Narrow Band Imaging and Fluorescence Cystoscopy in Detecting Non-Muscle Invasive Bladder Cancer: A Systematic Review and Diagnostic Meta-Analysis

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Bladder cancer, fluorescence, narrow band imaging (NBI).

Citation: EMJ Urol. 2018;6[1]:38-41. Abstract Review No. AR5.

Bladder cancer represents one of the most common malignancies diagnosed in both males and females, with an estimated 79,030 new cases and 16,870 estimated deaths in the USA in 2017.[1] It is important to monitor bladder cancer patients, given the high risk of both recurrence and progression, through regular endoscopic

surveillance with cystoscopy following the first transurethral resection of the bladder tumour (TURBT).[2] Although conventional white light imaging (WLI) cystoscopy and TURBT are the standard methods for detecting urothelial tumours,[2] the use of WLI could lead to approximately 10–20% of lesions that are not readily visible being overlooked.[3] As a result, novel technologies are being developed in order to improve the detection rate and allow a more accurate diagnosis that can positively impact patient prognosis.

Blue light cystoscopy, also known as photodynamic diagnosis (PDD) fluorescence cystoscopy, was first described in 1964[4] and has gained popularity over the years.[5]

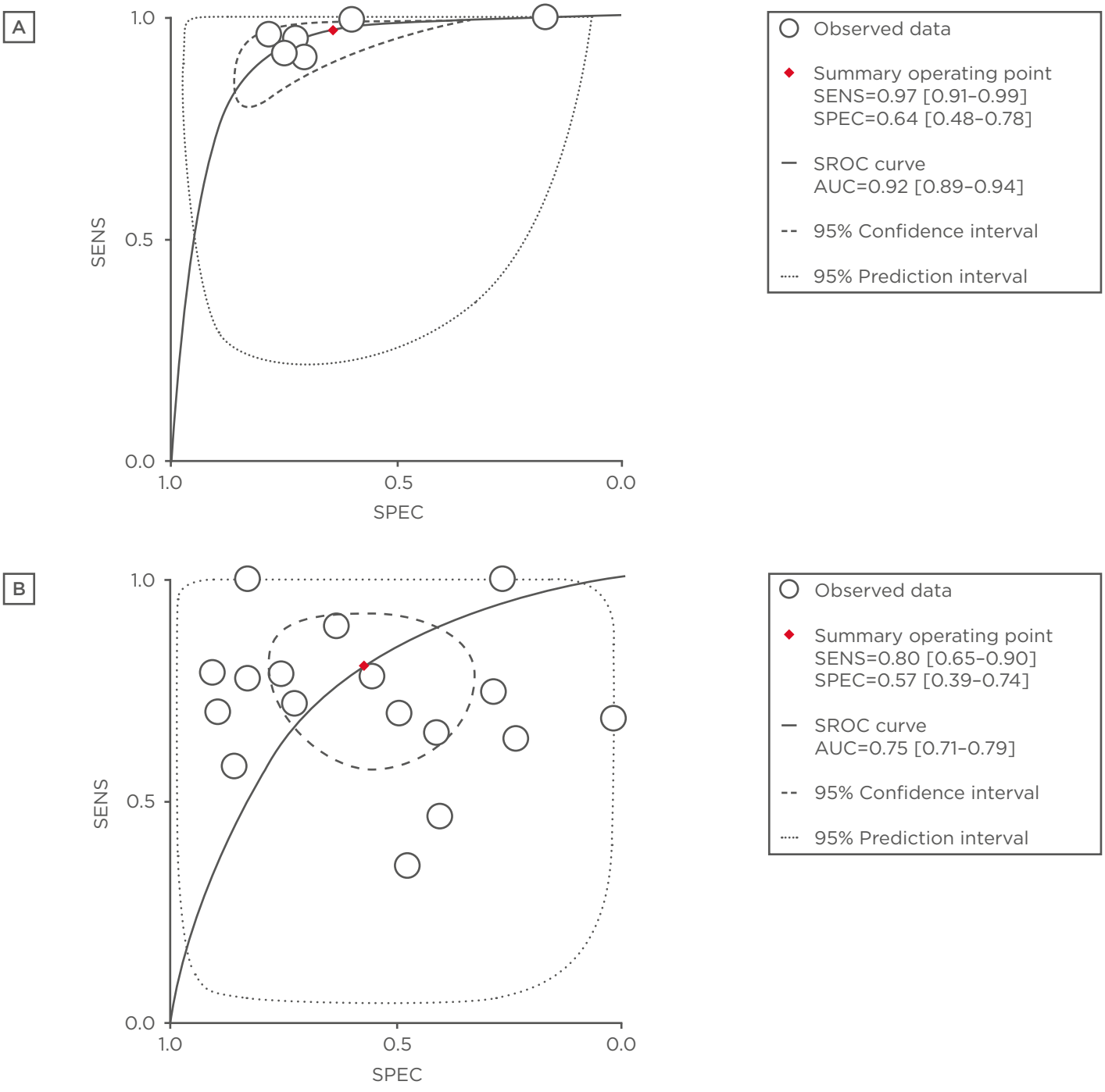

Figure 1: Hierarchical summary receiver operating characteristic plot (solid line) and summary point with 95% confidence interval (circled area) of A) narrow band imaging, B) white light imaging, and C) photodynamic diagnosis, in predicting overall bladder cancer.

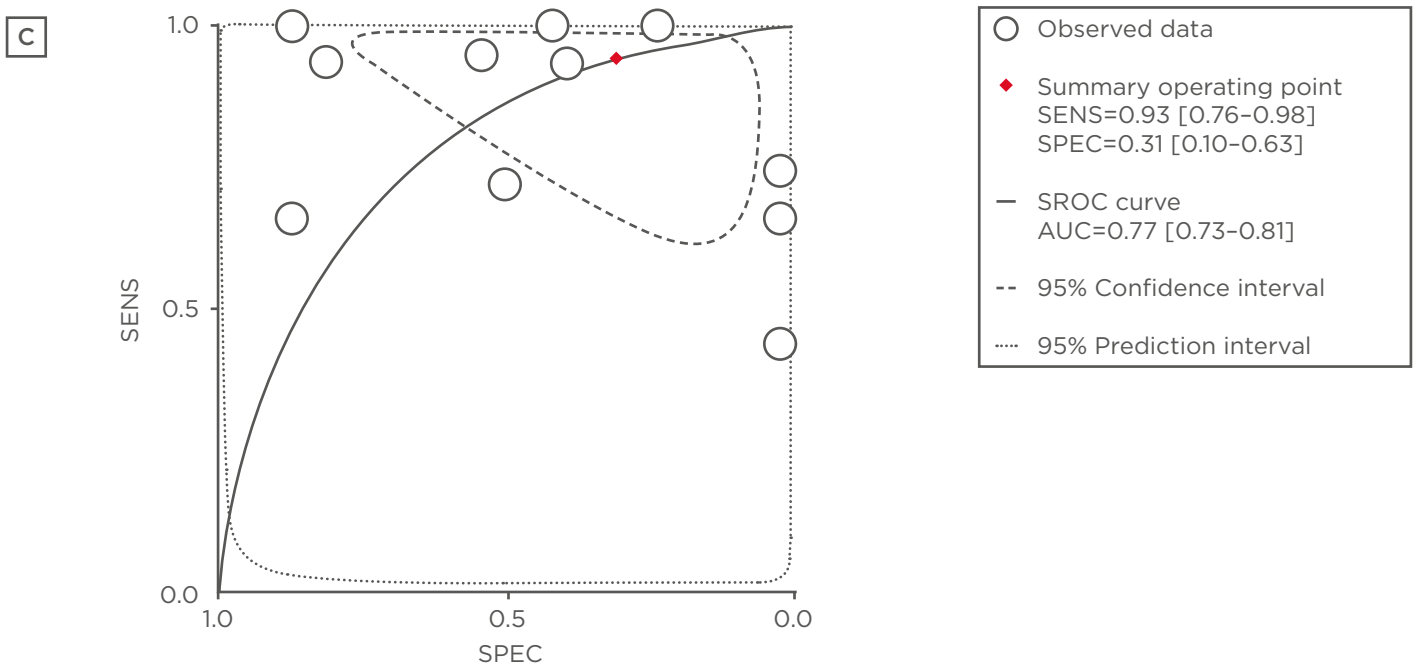

Figure 1 continued.

The dashed line is the line of no discrimination (area under the curve of 0.5, indicating a worthless test).

AUC: area under the curve; SENS: sensitivity; SPEC: specificity; SROC: summary receiver operating characteristic.

Narrow band imaging (NBI) is another valid technique, which works by filtering the white light into specific light wavelengths that are absorbed by haemoglobin, and only penetrate the surface of human tissue, enhancing the visualisation of mucosal vasculature and highlighting neoplastic neoangiogenesis of urothelial tumours.[2] The aim of the present study was to accomplish a comprehensive systematic review and diagnostic meta-analysis to compare oncological outcomes, as well as evaluate the diagnostic accuracy of WLI, NBI, and PDD for detecting overall bladder cancer at an individual biopsy level. Eligible studies were divided into three categories: first, randomised clinical trials comparing 5-aminolevulinic acid versus WLI; second, randomised clinical trials comparing hexaminolevlinate versus WLI; and third, randomised clinical trials comparing NBI versus WLI. No trials were excluded. The study is registered with PROSPERO, number CRD42017069333.

The systematic literature search initially yielded 1,606 articles. After removing 532 duplicates, the screening of the remaining 1,074 titles and abstracts generated 326 potentially eligible original articles. The pooled data showed a sensitivity of 0.93 (95% confidence interval [CI]: 0.76–0.98), 0.97 (95% CI: 0.91–0.99), and 0.80 (95% CI: 0.65–0.90) for PDD, NBI, and WLI, respectively, and a pooled specificity of 0.31 (95% CI: 0.10–0.63), 0.64 (95% CI: 0.48–0.78), and 0.57 (95% CI: 0.39–0.74) for PDD, NBI, and WLI, respectively. The heterogeneity of WLI was significant for specificity (Chi-square: p=0.00; I^2: 98.59) and sensitivity (Chi-square: p=0.00; I^2: 98.69); of NBI for specificity (Chi-square: p=0.00; I^2: 87.20) and sensitivity (Chi-square: p=0.04; I^2= 57.69); and of PDD for specificity (Chi-square: p=0.00; I^2: 99.35) and sensitivity (Chi-square: p=0.00; I^2= 99.70). The diagnostic odds ratios for PDD, NBI, and WLI were 6.18 (95% CI: 0.57–66.40), 54.11 (95% CI: 27.73–105.60), and 5.31 (95% CI: 1.74–16.22), respectively. The derived area under the curve from the hierarchical summary receiver operating characteristic showed an accuracy of 0.92 (95% CI: 0.89–0.94), 0.77 (95% CI: 0.73–0.81), and 0.75 (95% CI: 0.71–0.79) for NBI, PDD, and WLI, respectively (Figure 1).

In this diagnostic meta-analysis, it was demonstrated that PDD and NBI exhibited lower recurrence rates and greater sensitivity than WLI. These results provide a step forward in abandoning WLI for the diagnosis and follow-up of bladder cancer. Despite this,

patients who may benefit from WLI in terms of cost and efficacy must not be discriminated against, and PDD or NBI should replace standard cystoscopy.

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Dehydrated Human Amnion/Chorionic Membrane Wrapping of the Neurovascular Bundle During Robot-Assisted Laparoscopic Radical Prostatectomy Improves Postoperative Recovery of Erectile Function

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Disclosure: Dr Patel is a consultant for MiMex. The remaining authors have declared no conflicts of interest.

Keywords: Erectile dysfunction (ED), nerve regeneration, robot-assisted laparoscopic prostatectomy (RALP).

Citation: EMJ Urol. 2018;6[1]:41-43. Abstract Review No. AR6.

Robot-assisted laparoscopic prostatectomy (RALP) has become a standard treatment in the management of localised prostate cancer; however, erectile dysfunction (ED) and incontinence remain the major side effects of RALP, despite advances in surgical techniques. The incidence of postoperative ED ranges from 10–46% and the condition is the leading cause of patient dissatisfaction after RALP.[1] Several surgical refinements have been described to enhance functional recovery, including athermal neurovascular bundle (NVB) dissection and minimal NVB traction during nerve-sparing (NS) RALP.[1,2] Even in patients with good NS, there is a convalescence period due to surgical trauma-induced inflammation, neuropraxia, and nerve injury,[2] which leads to delayed functional recovery.

The use of growth factors and anti-inflammatory substances is a novel concept for the prevention of the inflammatory response and neuropraxia in NVB. Dehydrated amnion/chorion membrane (dHACM) contains numerous growth factors and anti-inflammatory mediators that have proven clinical benefits in nerve healing.[3,4] Our group was the first to propose enhanced NVB healing by application of dHACM in RALP patients.

Table 1: Number of men who achieved potency after robot-assisted laparoscopic prostatectomy analysis based on age categories and preoperative erectile function.

	Group I (Amniotic membrane) n=440	Group II (Control) n=440	p value
Irrespective of age, preoperative SHIM, and nerve spare	335/440 (76.1%)	292/440 (66.4%)	0.001*
Age ≤50 years	64/77 (83%)	52/67 (78%)	0.40
Age 51–60 years	174/218 (80%)	153/218 (70%)	0.02*
Age >60 years	97/145 (67%)	87/155 (56%)	0.05*
Nerve spare (irrespective of preoperative potency and age)			
Full nerve spare	253/325 (78%)	223/318 (70%)	0.025*
Partial nerve spare	82/115 (71%)	69/122 (59%)	0.018*
Preoperative potency (irrespective of nerve spare and age)			
No erectile dysfunction (SHIM ≥22)	266/336 (79%)	221/310 (71%)	0.02*
Mild-to-moderate erectile dysfunction (SHIM ≤21)	69/104 (66%)	71/130 (55%)	0.06
Age group with full nerve spare (irrespective of preoperative potency)			
Age ≤50 years	46/53 (87%)	38/50 (76%)	0.15
Age 51–60 years	134/164 (82%)	120/166 (72%)	0.04*
Age >60 years	73/108 (68%)	65/102 (64%)	0.55
Age group with full nerve spare and normal preoperative erectile function (SHIM ≥22)			
Age ≤50 years	38/41 (93%)	27/34 (79%)	<0.001
Age 51–60 years	113/134 (84%)	93/120 (78%)	0.16
Age >60 years	53/74 (72%)	48/73 (66%)	0.44

SHIM: sexual health inventory for men.

*statistically significant.

In our preliminary study of 58 patients, we found that NVB wrapping with dHACM accelerated continence and potency recovery at 8 weeks.[5] The current study represents further testing of our hypothesis in a larger patient population with up to 18 months follow-up.

In this study, all consecutive men who received dHACM wrapping of the NVB during RALP between August 2013 and December 2016 were analysed (Group I [n=440]). The control group was selected by propensity score matching for age, Gleason score, D'Amico risk category, and preoperative sexual health inventory for men (SHIM) score (logistic regression nearest neighbourhood method at 1:1 ratio). Oncological and functional outcomes were compared between the two groups. Factors affecting potency recovery were analysed using univariate and multivariate logistic regression analyses.

When the study groups were compared, there was no significant difference in continence (0–1 pad/day) rates at a median follow-up of 18 months (97.7% versus 97.2%; p=0.66). As compared to the control group, potency rates at follow-up were significantly higher (76.1% versus 66.4%; p=0.001; Table 1) and potency recovery was significantly faster (4.1 versus

5.7 months; p=0.001) in the dHACM group irrespective of age, preoperative erectile function, and degree of NS. On multivariate analysis, age, preoperative potency, NS status, and dHACM nerve wrapping were found to be independent predictors of potency recovery.

The subgroup analysis showed that preoperatively potent (SHIM score ≥22) patients <50 years of age with complete NS benefited most from dHACM (postoperative potency of 93% versus 79%; p<0.001; Table 1). Furthermore, dHACM increased the potency rates whether a full bilateral or a partial NS was performed; this implied that dHACM graft can exert its healing effect on all branches of the NVB that can be preserved. Therefore, dHACM may serve as a valuable tool to optimise NS outcomes in high-risk prostate cancer patients whenever partial NVB preservation is more feasible than full NS due to concerns with increased surgical margin positivity risk. Future randomised studies will better clarify the clinical benefits of dHACM in functional outcomes after RALP.

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Dablaca-11: Photodynamic Diagnosis in Flexible Cystoscopy: Initial Findings in a Randomised Controlled Trial

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Keywords: Flexible cystoscopy, non-muscle invasive bladder cancer (NMIBC), photodynamic diagnosis (PDD).

Citation: EMJ Urol. 2018;6[1]:43-44. Abstract Review No. AR7.

INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) can be treated by organ-sparing transurethral resection of bladder tumour (TURBT) but has a high risk of recurrence and probability of grade and stage progression. If recurrence is diagnosed at a very early stage, it can be treated in the outpatient clinic.[1] As a standard, white light (WL) flexible cystoscopies are used in the surveillance programme. Photodynamic diagnosis (PDD) is an optical technique that

uses fluorescence as a contrast mechanism to indicate pathologic tissue. Studies on PDD-guided TURBT have shown that up to 15% of non-invasive tumours and approximately 30% of flat carcinoma *in situ* may be overlooked by conventional WL cystoscopy.[2] This randomised study aimed to investigate whether the use of PDD could reduce the number of recurrences when performing a follow-up flexible cystoscopy in the outpatient clinic. This abstract, presented at the 2018 European Association of Urology (EAU) Congress, presents the initial results of the treatment at the time of enrolment and randomisation.

MATERIALS AND METHODS

From February 2016–September 2017, 605 patients from three urological departments in Denmark were studied. All patients followed the Danish surveillance programme for NMIBC. Patients were randomised 1:1 to either an intervention group where hexaminolevulinate (Hexvix®; Photocure, Oslo, Norway) was instilled in the bladder 1 hour before the cystoscopy with PDD video cystoscope (PDD 11272 VPI, D-Light C-Light Source; Karl Storz, Tuttlingen, Germany), or a control group where cystoscopy was performed with a WL flexible cystoscope. In both patient groups, solitary or small (<1 cm) multiple recurrences, as well as suspect mucosa, were biopsied or fulgurated directly in the flexible procedure if possible or scheduled for a new TURBT.

RESULTS

A total of 304 patients were allocated to the intervention group (flexible PDD) and 301 to the control group (flexible WL). Approximately half of all patients in both groups were recurrence free (intervention group, n=157, and control group, n=150). The number of patients treated in the outpatient clinic was higher in the intervention compared to the control group. Thus, significantly fewer patients were scheduled for a TURBT in the intervention group (Table 1).

CONCLUSION

These initial results indicate that PDD-guided flexible cystoscopy can reduce the need for TURBT when biopsy and fulguration of small tumours is possible in the outpatient clinic. Further follow-up data on long-term recurrence will be needed to estimate the clinical impact regarding the reduction of recurrence risk and repeated procedures.

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Table 1: Number of patients receiving treatment at time of enrolment and randomisation.

Treatment of papillary tumours*	**Outpatient**	**TURBT**	**Normal**	**Total**
Control group	76	75	150	301
Intervention group	95	52	157	304
Total	171	127	307	605
Treatment of suspicious areas*	**Coagulation**	**Biopsy**	**Normal**	**Total**
Control group	15	21	265	301
Intervention group	31	35	238	304
Total	46	56	503	605

In the control group, cystoscopy was performed with a white light flexible cystoscope. In the intervention group, hexaminolevulinate was was instilled in the bladder 1 hour before the cystoscopy with a photodynamic diagnosis video cystoscope.

*p value: <0.05

TURBT: transurethral resection of bladder tumour.

A Prospective Analysis Concerning the Limited Clinical Consequences of Positive Microbial Cultures After Transurethral Resection of the Prostate

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Clinical infection rate, fever, postoperative bacteriuria, septicaemia, transurethral resection of the prostate (TURP).

Citation: EMJ Urol. 2018;6[1]:45-46. Abstract Review No. AR8.

INTRODUCTION AND OBJECTIVES

A prospective study was set up to investigate the correlation between clinical infection rate (fever or septicaemia) and postoperative bacteriuria in patients undergoing transurethral resection of the prostate (TURP) because the clinical significance of postoperative bacteriuria after TURP remains unclear.[1-4] Additional irrigation fluid cultures, blood cultures, and prostate tissue cultures were also cultivated to evaluate the clinical consequences in cases of a positive culture.

MATERIALS AND METHODS

After ethical committee approval, 506 consecutive patients undergoing TURP between August 2008 and September 2015 were prospectively investigated. A urine analysis (preoperative, at hospital discharge, and 3 weeks postoperative) was performed in addition to an analysis of the blood culture or irrigation fluid and the resected prostatic tissue. Microbial cultures were scored by microbiologists as 0 (not significant), 1 (mildly significant), or 2 (significant). Clinical infectious complications were recorded and treated by antibiogram. Antibiotic prophylaxis was only used in patients with preoperative bacteriuria or a preoperative indwelling catheter. The most commonly used antibiotics were fluoroquinolones (89.5%), followed by amoxicillin (6.0%).

RESULTS

Forty-two patients (8.2%) had significant preoperative bacteriuria. The most common organisms were *Escherichia coli* (28.2%) and *Klebsiella* (21.7%). Fifty-eight patients (7.3%) had significant postoperative bacteriuria at the time of hospital discharge, with *Enterococcus faecalis* the most frequent organism (29.2%), followed by *Klebsiella* (13.2%) and *E. coli* (13%). Thirty-six patients (7.1%) had significant postoperative bacteriuria 3 weeks after TURP, with *E. faecalis* (44.4%) the most frequent bacteria, followed by *E. coli* (36.1%). Thirty-one patients (6.1%) had significant positive blood cultures (at the recovery unit). *E. coli* and haemolytic *Streptococci* were the most frequent organisms (each 19.4%). Twenty-four patients (4.7%) had significant positive irrigation fluid cultures (upon arrival at the ward). *E. coli* was the most commonly found organism (29.2%), followed by *E. faecalis* (25%). Forty-seven patients (9.3%) had a significant positive prostate tissue culture, with *E. faecalis* (36.1%) and *Staphylococci* (14.9%) the most commonly found organisms. Eighteen patients (3.6%) had uncomplicated fever during or after hospitalisation and 1 patient (0.2%) had septicaemia and a high-degree fever (>38.5°C).

CONCLUSION

A low rate of clinical infectious complications (fever or septicaemia) was observed (3.6%) despite the high rate of postoperative bacteriuria at time of discharge (6.9%) and after 3 weeks (7.1%). The high numbers of positive blood (6.1%), irrigation fluid (4.7%), and prostate tissue cultures (9.3%) were also of limited clinical relevance. In our opinion, postoperative

bacteriuria and positive blood cultures in the absence of clinical infection should not be treated. Additional studies are needed to support our findings.

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New Challenges for an Old Issue: Considering the Real Aetiology of Recurrent Haematuria: A Urinary System Pathology or a Complication of Antiplatelet and/or Anticoagulant Treatment?

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INTRODUCTION AND OBJECTIVES

In today's world of innovation and technology, which provides the very best opportunities for healthcare professionals, everyone wants to have the best health status, and the scope to explore the aetiological roots of different healthcare problems is limitless.

Haematuria is an ancient issue but it still generates new challenges, especially for patients who are dealing with other health problems. In our study, which included 2,500 cases of haematuria, we aimed to provide a retrospective evaluation of the aetiological and pathological properties of patients with recurrent haematuria attending our urology clinic. It is essential to identify whether haematuria is a real indicator of a prominent urological disease or just a sign of the complications of the patient's treatments.

MATERIALS AND METHODS

While organising the retrospective study, 2,500 patients with recurrent haematuria, aged 27–93 years with a mean age of 58.2 years, and who attended the clinic within the last 87 months, were re-evaluated. A total of 1,312 patients with recurrent microscopic haematuria (412 [31.4%] males) and 1,188 patients with recurrent macroscopic haematuria (354 [29.8%] males), were evaluated retrospectively, and 934 underwent cystoscopy. The number of patients who used antiplatelet and/or anticoagulant treatment totalled 1,680 (67.2%); these patients were examined to find out whether the aetiology of haematuria was due to urinary system pathology or the result of complications from antiplatelet and/or anticoagulant treatment.

RESULTS

A total of 270 (20.6%) patients with microscopic haematuria and 214 (16.3%) with

macroscopic haematuria revealed urolithiasis aetiology. Furthermore, 116 (8.9%) of the microscopic haematuria patients and 92 (7.7%) of the macroscopic haematuria patients were diagnosed with tumoural lesions of the bladder following ultrasonography. However, 33 of the cases suspected of having tumoural lesions had no lesions present, but were instead diagnosed with haematoma. Twenty-eight (3.9%) of the tumoural lesions were found to be pT2 on pathological examination, with the remaining lesions being pT1G2–pT1G3. Thirty-one (2.4%) microscopic haematuria and 27 (2.3%) macroscopic haematuria cases revealed upper urinary tract transitional cell carcinoma. In 41 (4.4%) of the 934 patients undergoing cystoscopy, tumoural lesions missed during ultrasonography were found in the bladder. Of 2,500 cases, only 30 (1.2%) had renal cell carcinoma as an aetiology of recurrent haematuria. Fifty-one male patients with recurrent haematuria were diagnosed with prostate adenocarcinoma. Only 802 (32.0%) patients with recurrent haematuria revealed a real urinary system pathology, and 657 of these patients were using antiplatelet and/or anticoagulant treatment. In 792 (47.1%) of the 1,680 patients receiving antiplatelet and/or anticoagulant treatment, no urinary system pathology was detected and recurrent haematuria was accepted to be due to complications of the antiplatelet and/or anticoagulant treatment.

CONCLUSION

Recurrent haematuria is a challenging problem that always requires detailed evaluation. In cases of no urinary system pathology, recurrent haematuria can be seen as a complication during antiplatelet/anticoagulant treatment in up to 47.1% of patients. This retrospective evaluation of 87 months, containing valuable incidence data, can be used as a vital source for international guidelines of urology.

Positive Surgical Margins After Robot-Assisted Radical Prostatectomy in the Multiparametric Magnetic Resonance Imaging Era: The Experience of a High Volume Third Referral Centre

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INTRODUCTION

The use of multiparametric-magnetic resonance imaging (mpMRI)-guided intraoperative frozen-section analysis showed its effectiveness in reducing positive surgical margin (PSM) rates during nerve-sparing (NS) robotic-assisted radical prostatectomy (RARP) for organ-confined prostate cancer.[1]

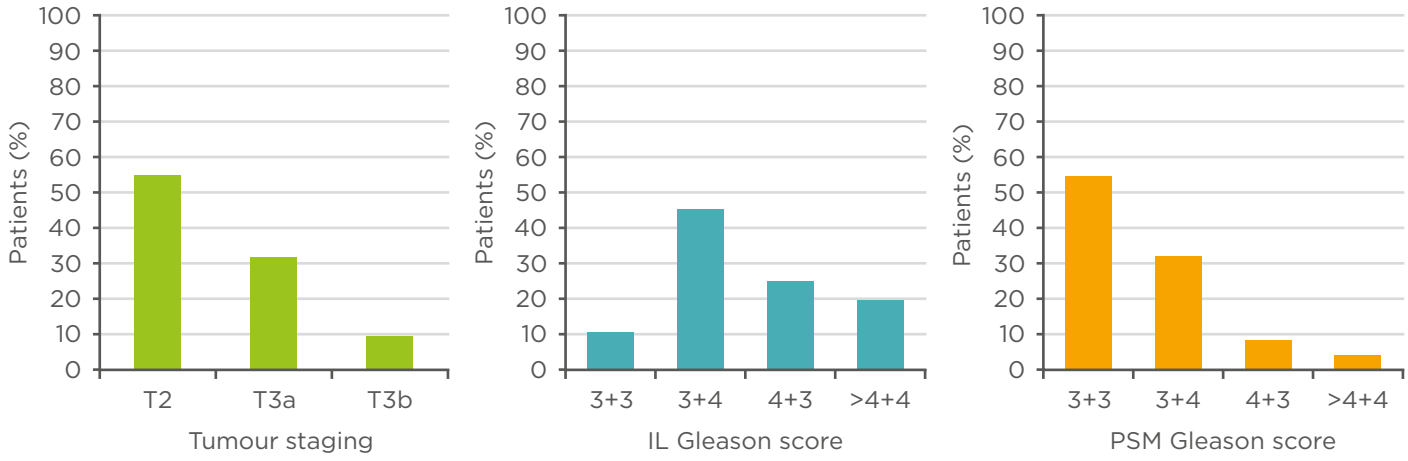

Figure 1: Patient distribution according to the tumour staging, the index lesion Gleason score, and the Gleason score assessed at the level of the positive surgical margins (analysed for 22 out of 56 patients).

IL: index lesion; PSM: positive surgical margins.

The aim of the current study was to investigate the subgroup of patients with PSM occurring in a different site respective to the mpMRI index lesion (IL) location and to determine potential predictors of this event.

METHOD

From January 2014–April 2017, a total of 1,788 consecutive patients were subjected to RARP for prostate cancer. A preliminary mpMRI was performed on 98% of these patients. All patients received intraoperative frozen-section analysis to determine possible PSM. All data were prospectively collected in a customised database and retrospectively analysed. The primary outcome investigated was the concordance between PSM side and the location of the IL, as detected by the mpMRI. Univariable and multivariable analyses were used to identify potential predictors for PSM occurring distant to the mpMRI-IL position.

RESULTS

PSM were found in 187 (10.67%) patients with available preoperative mpMRI having received RARP. We considered a subgroup of 56 (29.90%) patients for analysis, in whom PSM occurred in a different site respective to the mpMRI IL location. In 76.80% of this subgroup, patients presented a Prostate Imaging Reporting and Data System (PI-RADS) score of 4 or 5 IL, while 11 patients (19.60%) had evidence at mpMRI of multifocal significant disease (secondary lesion PI-RADS >3). Out of 56 patients, the procedure was carried out as non-NS in 3 patients (5.10%); monolateral NS surgery was performed in 14 patients (25.00%), and bilateral NS in 39 (69.90%) patients.

In 85.80% of the cohort, a PSM occurred posterolaterally, and in the remaining 14.20% anteriorly.

Twenty (35.70%) patients of these 56 had evidence of PSM at the FSA, but in 17 (85.00%) the PSM was described as focal (<1 mm of extension).

Patient distribution according to the tumour staging, the IL Gleason score (GS), and the GS assessed at the level of the PSM (analysed for 22 out of 56 patients) is reported in Figure 1. At multivariable analysis, low (3+3) and intermediate (3+4) preoperative GS were significantly associated with the occurrence of PSM on a different site respect to the IL location ($p<0.05$).

CONCLUSION

The results of this study demonstrated that the introduction of the mpMRI in the preoperative workout had lowered the rate of PSM. However,

in some patients subjected to NS, discordance between the site of PSM and MRI lesions still exists. This issue has been described, in particular, for low–intermediate risk patients due to a more aggressive NS procedure performed distant from the mpMRI IL.

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Unintended Consequences of Decreased Prostate Specific Antigen-Based Prostate Cancer Screening

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INTRODUCTION

In May 2012, the U.S. Preventive Services Task Force issued a Grade D recommendation against prostate-specific antigen (PSA)-based screening for prostate cancer diagnosis. Since then, epidemiologists have raised concerns that an unintended consequence of the recommendation could be a problematic increase in high-risk disease and its subsequent impact on the risk of prostate cancer progression and mortality.

Dr Thomas Ahlering, a urologic oncologist from the University of California, Irvine, California, USA, presented the first study that utilises high-risk oncologic metrics to assess the impact that the Grade D recommendation has on high-risk disease presentation at the time of radical prostatectomy. The case series analysis utilised data from 19,602 patients undergoing robot-assisted radical prostatectomy from nine high-volume institutions throughout the USA. The potential effect of reduced PSA screening was assessed by comparing the absolute number of patients (at each institution and collectively) with seminal vesicle invasion, lymph node metastasis, and Gleason score 9 and 10 cancers 4 years pre versus post recommendation.

RESULTS

Compared to the 4-year average, pre (October 2008–September 2012) versus post

recommendation (October 2012–September 2016), there was a 22.6% reduction in surgical volume, and, as anticipated, an increase in median PSA (from 5.1 to 5.8 ng/mL), and an increase in mean age (from 60.8 to 62.0 years). However, there was a near-doubling in the absolute number of Gleason score 9 and 10 cancers, and a tripling of nodal metastases. The 1-year biochemical recurrence post-radical prostatectomy rose from 6.2% to 17.5%.

CONCLUSION

One of the strengths of this study was the use of propensity score matching for age and PSA across the screening eras. Not only do the authors report an increase in more aggressive disease in the post recommendation era but also a stepwise increase in high-risk disease each year subsequent to the recommendation. In other words, for any given age and PSA, propensity matching suggests that there may be a trend for more aggressive disease post recommendation. While changes in referral pattern and/or the use of radiation therapy may contribute to some of this impact, these limitations need to be considered within the context of these findings. The current study joins the growing body of literature in raising concerns of a shift towards high-risk disease, associated increases in biochemical recurrence, and secondary interventions (and their side effects) following the U.S. Preventive Services Task Force recommendation.

Addendum in: EMJ Urol. 2018;6[1]:32–50. Due to human error on EMJ's part, an Abstract Review was not initially published in this journal. The Abstract Review can be found by clicking here.

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Advances and Perspectives in Urinary Bladder Cancer Nanotherapy

EDITOR'S PICK

This issue's Editor's Pick is an informative review from Fávaro and colleagues discussing the recent advances in the treatment of non-muscle invasive bladder cancer. Treatment remains a challenge due to the recurrence and progression of the disease, and it is crucial to develop innovative drug delivery strategies. Recent progress achieved via nanotherapy to provide a sustained and controlled drug delivery directly to the target site of application is explored and is shown to be a promising therapeutic approach.

Samantha Warne

Editor

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Abstract

Bladder cancer treatment remains a challenge in the pharmaceutical field due to the recurrence and progression of the disease, as well as the pronounced side effects associated with the available therapeutic modalities. Although important strategies have been investigated in different clinical trial phases, efficient and well-tolerated treatment approaches need to be developed to improve therapeutic efficacy and the quality of life for bladder cancer patients. This review discusses conventional protocols used in the clinical setting, detailing the use of Bacillus Calmette–Guérin, new immunomodulators, and drug delivery systems. New therapeutic approaches have been investigated with the aim of better therapeutic efficacy with low rates of recurrence and progression

of non-muscle invasive bladder cancer and muscle invasive bladder cancer. Therefore, this review highlights the progression of therapy with the use of conventional treatments and the recent progress achieved from the use of innovative strategies, such as nanoparticles for sustained, controlled drug delivery and increased drug uptake by tumour cells.

INTRODUCTION

Overview of Bladder Cancer

Bladder cancer is an important type of cancer worldwide. The European Association of Urology (EAU) considers bladder cancer the eleventh most common cancer diagnosed worldwide.[1,2] The American Association for Cancer Research (AACR) estimated that approximately 79,030 new cases of bladder cancer would be diagnosed in the USA in 2017 (60,490 cases in men and 18,540 in women) with approximately 16,870 deaths resulting from bladder cancer (12,240 men and 4,630 women).[3]

More than 70% of bladder cancer is superficial (i.e., non-muscle invasive bladder cancer [NMIBC]) and classified into three stages: pTis (flat carcinoma *in situ*), pTa (non-invasive papillary carcinoma), and pT1 (tumour invading the mucosa or submucosa of the bladder wall). Despite the prognosis associated with NMIBC, almost 50% of patients will experience recurrence of their disease within 4 years of their initial diagnosis and 11% will progress to muscle invasive bladder cancer (MIBC).[2]

Non-Muscle Invasive Bladder Cancer

The primary therapy for high-grade NMIBC is based on surgery in the form of transurethral resection of the bladder tumour followed by intravesical immunotherapy with Bacillus Calmette–Guérin (BCG).[1,2] The response induced by BCG reflects induction of a T helper Type 1 response to prevent recurrence and to reduce tumour progression.[1,2] However, BCG treatment is associated with therapeutic failure in up to 50% of patients and several side effects occur in up to 90% of patients.[2]

The treatment of NMIBC remains a challenge in the pharmaceutical field due to the recurrence and progression of the disease, as well as the pronounced side effects that are still associated with the available therapeutic modalities. Although important strategies have been investigated in different preclinical studies and clinical trials, it is crucial to develop innovative drug delivery platforms that allow intravesical drug administration, avoiding the progression of NMIBC to MIBC and thus improving patient quality of life.[4]

TREATMENT MODALITIES

Immunomodulators

In 2014, a literature review demonstrated that transurethral resection with adjuvant intravesical chemotherapy or immunotherapy is the standard treatment option for NMIBC.[5] Interferon (IFN)-α as adjuvant therapy had limited efficacy, but BCG monotherapy was suggested as first-line treatment. However, cancer progression or recurrence was a common outcome, and when treated with radical cystectomy it was associated with significant morbidity and mortality, as well as low quality of life. Unfortunately, chemotherapeutic treatment is not effective after BCG failure.[6] There is a lack of efficacious treatment options for patients with NMIBC recurrence or progression after initial BCG treatment.

In 2016, atezolizumab, an immune checkpoint inhibitor (T cell), was approved in metastatic urothelial carcinoma; later, in 2017, nivolumab was also approved.[7] Programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) checkpoint inhibitors have achieved durable clinical responses in a subset of previously treated and treatment-naïve patients with metastatic urothelial carcinoma. The combination of PD-1 and cytotoxic T-lymphocyte antigen 4 has successfully improved response rates, including for bladder cancer.[8]

BCG-cell wall skeleton (CWS) represents an alternative to the use of live BCG. However, many problems, such as low water solubility and a high molecular weight, have been identified. In order to overcome these obstacles, Nakamura et al.[9] developed lipid nanoparticles for BCG loading.

It is known that IFN-α is effective against carcinoma *in situ* and is also a prophylactic agent after transurethral resection in patients with bladder cancer, which involves the stimulation of the T helper 1 immune response by IFN when associated with BCG.[10] Patients who failed BCG treatment were treated with IFN and BCG in lower doses than the conventional protocols for BCG alone.[11,12]

In a study with 236 patients with frequently recurring Ta or T1 Grade 1–2 NMIBC, treated with mitomycin C instillations followed by monthly BCG, significantly reduced long-term disease recurrence in relation to alternating instillations of BCG and IFN-α2b. Therefore, the combined therapy of BCG with IFN-α offers an appreciable clinical benefit compared with BCG alone.[10]

Protein Aggregate Magnesium-Ammonium Phospholinoleate-Palmitoleate Anhydride Immunomodulator

The protein aggregate magnesium-ammonium phospholinoleate-palmitoleate anhydride (P-MAPA) comprises a non-linear biopolymer produced by the fungus *Aspergillus oryzae* during the fermentation process. Studies conducted with P-MAPA in animal models showed this compound to have both anti-tumoural and anti-infectious effects.[13-15] The main mechanism by which P-MAPA realises its pharmacological effects comprises the modulation of both immunomodulatory processes and biological responses.

The anti-tumour activity of P-MAPA was evaluated *in vivo* using a bladder cancer model induced in female Fischer 344 rats.[16,17] The anti-tumour assays revealed that P-MAPA increased toll-like receptor (TLR)2, TLR4, and p53 levels. Moreover, it was more effective in treating bladder cancer compared to BCG.[16,17] Garcia et al.[18] investigated the biological responses due to the association of P-MAPA with flutamide with the aim of potentiating the anti-tumour response compared to BCG, the most commonly used therapy for NMIBC. Data showed that P-MAPA was able to activate the innate immune response via TLR2 and TLR4; this resulted in an increase of IFN signalling compared to BCG, which is consistent with the superior efficacy of P-MAPA in relation to BCG. In this protocol, there was a complete regression in both neoplastic (60% of the animals) and benign tumours (40% of the animals). P-MAPA has demonstrated the ability of activating the innate immune response via TLR2 and TLR4, and also to increase IFN signalling; thus, it may represent a promising alternative for treatment of NMIBC.

P-MAPA intravesical immunotherapy led to distinct activation of the TLR2 and TLR4-mediated innate immune system by increasing the IFN signalling pathway (TRIF-dependent pathway). P-MAPA therapy was found to be more effective in NMIBC treatment than BCG. P-MAPA immunotherapy increased wild-type p53 protein levels with nitric oxide-induced apoptosis and the upregulation of BAX. Therefore, P-MAPA immunotherapy is an important therapeutic strategy for NMIBC, offering a new perspective for the treatment of patients that are refractory or resistant to BCG intravesical therapy.[19] Interesting results were observed when using the combination of P-MAPA with cisplatin (CIS) and doxorubicin (DOX).[20]

DRUG DELIVERY SYSTEMS

Nanoparticulated Delivery Systems

In this important area of nanomaterial, some reviews have been published.[21-25]

Liposomes

A study evaluated the anti-tumour effect of free BCG-CW and R8-liposome-BCG-CWS using a bladder carcinogenesis model induced in Fischer 344 rats by N-butyl-N-(4-hydroxybutyl)-nitrosamine intravesical administration. The results demonstrated that both free BCG-CW and R8-liposome-BCG-CWS decreased carcinoma incidence and number of tumours compared to untreated animals.[26]

Duplex dsP21-322 and its chemically modified variants are examples of RNA-based drugs that inhibit cancer cell growth by inducing expression of tumour suppressor p21WAF1/CIP1 (p21). The 20-fluoro-modified derivative (dsP21-322-2'F) was encapsulated into lipid nanoparticles for intravesical delivery.

The therapeutic effect of dsP21-322 in an orthotopic model of bladder cancer with lipid nanoparticles, based on formulations used in RNA interference-based therapies consisting of polyethylene-glycol (PEG)-stabilised unilamellar liposomes built with lipid 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane, confirmed p21 induction (regression or disappearance of tumour in 40% of the treated mice), cell-cycle arrest, and apoptosis in an *in vitro* study, following treatment with lipid nanoparticle dsP21-322-2'F.[27]

BCG-CWS was used to replace live BCG as a bladder cancer drug encapsulated in a liposome. In a functional evaluation, CWS-nanoparticles were efficiently taken up by mouse bladder tumour cell line (MBT-2) cells *in vitro* and the nanoparticle formation inhibited tumour growth in mice with MBT-2 tumours.[28]

Another review considered the current status of intravesical liposomes or liposomal-mediated drug delivery for the treatment of interstitial cystitis (also known as painful bladder syndrome) and overactive bladder.[29] Flow cytometry analysis demonstrated that the uptake of liposomes at 37°C by cultured human UROtsa cells was via clathrin-mediated endocytosis.[30] Application of liposome and micelle-based formulations used in the delivery of platinum-based anti-cancer drugs in clinical trials found an enhancement in the treatment of cancers.[31]

The introduction of cholesteryl-PEG into the cationic liposomes showed a significant enhancement in cellular uptake by the efficient elimination of the aggregation process. The authors suggested that by incorporating cholesteryl-PEG into cationic liposomes it was possible to achieve both stability in urine and effective cellular uptake.[9] The lyso-thermosensitive liposomal DOX (LTLD) (ThermoDox®, Celsion Corporation, Lawrenceville, New Jersey, USA), in combination with loco-regional mild hyperthermia (HT), was used for targeted drug delivery to the porcine bladder wall *in vivo*. The results demonstrated that DOX accumulation and distribution within the bladder wall was observed at concentrations higher than with free intravenous DOX by mild bladder HT combined with systemic delivery of LTLD.[32]

Generally, in the treatment of bladder cancer it is desirable to preserve the bladder rather than perform a partial or full cystectomy. Bladder cancer patients who express high levels of polo-like kinase-1 (PLK-1) are known to have a poor prognosis. In this direction, intravesical PLK-1 small interfering RNA (siRNA) was studied. siRNA/cationic liposomes (the cationic liposome used was DOTMA) suppressed the expression of endogenous PLK-1 in a time and dose-dependent manner within bladder cancer cells.[33] In an *in vivo* study using an orthotopic mouse model and the LUC-labelled bladder cancer cell line (UM-UC-3 LUC), PLK-1 siRNA was transfected into the cells, reducing PLK-1 expression and inhibiting the growth of BC.[34] The summary of these results is presented in Table 1.

Polymeric Nanoparticles

Poly-ε-caprolactone (PCL) derivative, PCL-*b*-P(PMA-*click*-MSA-*co*-PEGMA)-loading superparamagnetic iron oxide nanoparticles (SPION), and the pendant dicarboxylic groups in the hydrophilic shell were used to co-ordinate CIS. The new CIS-conjugated polymeric nanoparticles nanostructure (Pt–Fe–PN) is superparamagnetic and mucoadhesive. The authors suggested that Pt–Fe–PN is potentially a promising CIS delivery vehicle in combination with SPION-inducing HT for bladder cancer therapy.[35]

Martin et al.[4] developed poly(lactic-co-glycolic acid) (PLGA) nanoparticles functionalised with polyguanidinium oxanorbornene (PGON), a synthetic polymer able to mimic cell penetrating peptides that are not toxic to mammalian cells. Nanoparticles were developed for delivery of belinostat, an inhibitor of the histone deacetylase. *In vivo* murine experiments with xenograft tumours were performed for the evaluation of anti-tumoural responses. The results revealed that tumours treated with PGON nanoparticles containing belinostat were 77% smaller in volume compared to those of the control group (painful bladder syndrome).[4]

In another murine study, Martin et al.[36] functionalised the surface of PLGA nanoparticles with the mucoadhesive and positively charged polymer chitosan (CHI) in an attempt to improve the drug retention over the urothelium surface

and to enhance drug absorption through this tissue. Chitosan-derived nanoparticles containing survivin-siRNA (NP-siSUR-CH2.5) decreased tumour volume by around 65% and survivin expression by 75%.

Recently, the anti-tumour activities and the mechanisms of hyaluronan (HA)/CHI nanoparticles-aggregated heteronemin (HET) were studied. Pure HET increased early and total apoptosis and JC-1 monomer fluorescence; however, HA/CHI nanoparticles-aggregated HET induced higher apoptosis and JC-1 monomer rates than pure HET. These data strongly indicated that HA/CHI nanoparticle-aggregated HET would be a potential approach for the treatment of *in vivo* urothelial cancer.[37]

Cationic 1,2-dioleoyl-3-trimethylammonium propane/methoxypoly (ethyleneglycol) nanoparticles encapsulating DOX for intravesical therapy of bladder cancer were tested in a murine model. The treatment prolonged the residence and penetration of DOX in the bladder wall, with subsequent improvement in cellular uptake.[38] Self-assembled tumour-targeting hyaluronic acid-IR-780 nanoparticles for the photothermal ablation of cells over-expressing the HA receptor CD44 in bladder cancer showed high tumour selectivity, high efficacy, excellent bioavailability, and biocompatibility only for bladder cancer.[39]

In 2017, Canada-based biotechnology firm Sitka Biopharma Inc., Vancouver, Canada, with Cancer Research UK and Cancer Research Technology, London, UK initiated a Phase I clinical trial of STK-01 (hyperbranched polyglycerol docetaxel) for treatment of patients with NMIBC.[40] It is known that nano-diamino-tetrac(tetraiodothyroacetic acid) (NDAT) targets a receptor on integrin αvβ3; αvβ3 is expressed by cancer cells and dividing endothelial cells. The NDAT was covalently bound to a PLGA nanoparticle that is able to encapsulate CIS. CIS-loaded NDAT was administered to xenograft-bearing nude mice. The tumour volume reduction efficiency obtained by CIS-loaded NDAT was greater than NDAT without CIS, which, in turn, was greater than CIS alone.[41] Erdogar et al.[42] developed cationic nanoparticles composed of CHI and PCL for intravesical administration of mitomycin C inrats, avoiding toxicity. Histopathological analysis of the CS-PLC nanoparticles effect showed a localised and higher distribution into the bladder and no systemic drug distribution (Table 1).

Protein-Derived Nanoparticles

Paclitaxel, a poor water-soluble drug, was encapsulated in albumin-modified nanoparticles in order to increase drug water solubility and to improve drug delivery to target cells (Abraxane™, Celgene Corporation, Summit, New Jersey, USA). In Phase I and Phase II clinical trials, the nanoparticles exhibited low toxicity and systemic absorption in patients with refractory NMIBC (T1, Ta, or Tis stage).[43] ABI-009 (rapamycin) proved to be effective against colon and breast tumours in xenograft studies. In addition, ABI-009 exhibited low toxicology and good efficacy and has reached a combined Phase I and Phase II study for the treatment of NMIBC.[44]

Methotrexate-albumin was used in combination with CIS in the treatment of patients with bladder cancer in a Phase II study with a 27% response rate. Methotrexate-albumin has not been taken further for clinical studies.[45]

A long-term follow-up of a Phase II trial of intravesical nanoparticle albumin-bound paclitaxel for patients with recurrent NMIBC after previous intravesical BCG therapy demonstrated that 6 of the 28 patients remained cancer free, with a recurrence-free survival rate of 18%. The authors suggested that nanoparticle albumin-bound paclitaxel is a reasonable treatment option in this high-risk population.[46]

Silica-Based Nanoparticles

Silica-based nanoparticles modified with thiol groups provided stronger interactions with the bladder urothelium in relation to nanoparticles modified with hydroxyl and amino groups. Nanoparticles functionalised with thiol loaded with DOX demonstrated that thiol-functionalised mesoporous silica nanoparticles (MSN) are promising as a mucoadhesive and sustained drug delivery system in acidic conditions.[47]

Sweeney et al.[48] described the application of novel MSN functionalised with a peptide that specifically binds to bladder cancer cells, PEG-tetramethylrhodamine isothiocyanate-Gd2O3-

MSN, thus improving specificity. In an *in vivo* model, MSN instilled into bladders of tumour-bearing mice enhanced T1 and T2-weighted magnetic resonance imaging signals, improving the detection of the tumour limits. These facts support the idea that this targeted nanomaterial presents new options for premature detection and possible therapeutic intervention.

Thiolated silica nanoparticles retention on porcine bladder mucosa *in vitro*, following irrigation with artificial urine solution, was reported. After irrigation with artificial urine solution, the thiolated nanoparticles demonstrate significantly greater retention (Wash Out [WO]50 value: up to 36 mL) compared to non-mucoadhesive dextran (WO50: 7 mL) but have weaker mucoadhesive properties than CHI (WO50: 89 mL).[49]

A polydopamine-based surface modification method was used to prepare a targeted DOX-loaded MSN and peptide conjugation, which exhibited release kinetic profiles similar to DOX. Efficient anti-tumour effects of DOX-loaded nanoparticles by a mouse xenograft tumour model *in vivo* were demonstrated.[50] These data are discussed in Table 1.

Carbon-Based Materials

Many forms of carbon-based material, such as carbon nanotubes, graphenes, graphene oxide (GO), and carbon nanofibres, are useful in biological applications.[51,52] As for GO, the addition of specific groups to the carbon nanotubes surface may improve the solubility and decrease toxicity of these nanostructures.[53]

A Pt(IV)-based single-wall carbon nanotube (SWNT)-mediated pro-drug led to intracellular concentrations of Pt^{4+} six-fold higher than when the testicular carcinoma cell line (NTera-2) was treated with the free drug. In addition, the cytotoxicity induced by CNT-loaded carboplatin was significantly higher than that provided by the free drug.[21,54]

Pirarubicin (tetrahydropyranyl-adriamycin [THP]), associated with SWNT through phospholipid-branched polyethylene glycol, showed no side effects with SWNT alone or with SWNT-THP treatments on rat bladder cancer. *In vivo* studies with rat bladder cancer as *in situ* models constructed by N-methyl-N-nitrosourea intravesical installation showed apoptosis rates of 96.85% for SWNT-THP. No side effects were observed in the SWNT-THP group.[55]

In an animal model for NMIBC, in which 100% of animals from the cancer group presented with carcinoma with invasion of the lamina propria (pT1) and squamous metaplasia, the effects of reduced GO (rGO) was studied. The best histological recovery was found in the rGO/CIS/DOX group, showing 40% had flat hyperplasia, 40% had low-Grade intraurothelial neoplasia, and 20% had pTis. Taken together, it was suggested that GO had potential as a carrier system of chemotherapeutic agents, such as DOX, and as nanoformulation for bladder cancer treatment (Table 1).[51,56,57] A binary detection system for the simultaneous detection of miRNA and telomerase using the concept of integration of signal amplification by nicking with the photo-quenching ability of GO has been developed. The most important result in this report was that this approach can differentiate MIBC from NMIBC, which will benefit clinical decision-making for personal treatment.[58]

Metallic Nanoparticles

Intravesical administration of nanocrystalline silver (1%) in rats decreased urine histamine, bladder tumour necrosis factor-α, and mast cell activation without any toxic effect, and these activities could be useful for interstitial cystitis.[59] (-)-Epigallocatechin-3-gallate was physically attached onto the surface of gold nanoparticles (GNP), and the anticancer activity of the (-)-epigallocatechin-3-gallate-adsorbed GNP inhibited tumour cell growth by means of cell apoptosis in C3H/HeN mice subcutaneously implanted with murine bladder tumour-2 cells.[60]

A hydrogel formulation (CHI and β-glycerophosphate-magnetic nanoparticles of Fe_3O_4) improved intravesical BCG retention time after the application of the magnetic field in rats.[61] Castiglioni et al.,[62] using both bare and polyvinylpyrrolidone-coated silver nanoparticles on T24 bladder cells, showed that the two types of silver nanoparticles promoted morphological changes and cytoskeletal disorganisation. Previous studies have reported the application of modified GNP in bladder cancer.

Table 1: Properties of nanoparticles and their effects on *in vivo* experiments.

Nanostructure	Description	Subject	Comments
Liposome Maruf et al.,[26] 2016	R-8-liposome-BCG-CWS	Rats	Decrease carcinoma incidence.
Liposome Kang et al.,[27] 2012	Pegylated-Duplex dsP21-322 (RNA-based drug)	Mice	p21 induction (regression or disappearance of tumour in 40% of the mice), cell-cycle arrest, and apoptosis *in vitro* following treatment with lipid NP dsP21-322-2'F.
Liposome Nakamura,[28] 2016	BCG-CWS liposome	Mice	CWS-NP was efficiently taken up by MBT-2 cells *in vitro* and inhibited tumour growth in mice with MBT-2 tumours.
Liposome Nogawa et al.,[34] 2005	PLK-1/cationic liposome (the cationic liposome used was DOTMA)	Mice	siRNA/cationic liposomes (the cationic liposome used was DOTMA) suppressed the expression of endogenous PLK-1 in a time and dose-dependent manner within bladder cancer cells and inhibited the growth of bladder cancer.
Liposome Mikhail et al.,[32] 2017	The lyso-thermosensitive liposomal doxorubicin (LTLD, ThermoDox®) in combination with loco-regional mild HT	Porcine	DOX accumulation and distribution within the bladder wall was at higher concentrations than with free intravenous DOX by mild bladder HT combined with systemic delivery of LTLD.
Polymeric NP Martin et al.,[4] 2013	PLGA, PGON/ belinostat, inhibitor of the HDAC.	Mice	PGON NP containing belinostat showed a 77% reduction in tumour volume compared with the control group (PBS).
Polymeric NP Martin et al.,[36] 2014	PLGA/CHI-survivin-siRNA (NP-siSUR-CH2.5)	Mice	Survivin-siRNA (NP-siSUR-CH2.5) decreased tumour volume by around 65% and survivin expression by 75%.
Polymeric NP Jin et al.,[38] 2016	Cationic DPP/DOX	Mice	DPP/DOX prolonged the residence, penetration of DOX into the bladder wall, with subsequent improvement of cellular uptake.
Polymeric NP Lin et al.,[39] 2017	Lyaluronic acid (HA)-IR-780 NP	Mice	HA-IR-780 NP for photothermal ablation in over-expressing CD44 (the receptor for HA) bladder cancer showed high tumour selectivity, high efficacy, excellent bioavailability, and biocompatibility only with bladder cancer.
Polymeric NP Sudha et al.,[41] 2017	PLGA/NDAT targets a receptor on integrins	Mice	NDAT-CIS was administered to xenograft-bearing nude mice and tumour volume reduction efficiency obtained was greater for NDAT-CIS than for NDAT without CIS, which, in turn, was greater than CIS alone.
Polymeric NP Erdogar et al.,[42] 2014	Cationic NP composed of CHI and PCL	Rats	CHI-PLC NP effect showed a localised and higher distribution into the bladder and no systemic drug distribution was found.
Protein-derived NP McKiernan et al.,[43] 2014	Albumin-modified NP	Phase I and in a Phase II clinical trials	Abraxane exhibited low toxicity and systemic absorption in patients with refractory NMIBC.
Protein-derived NP Bolling et al.,[45] 2006	MTX-HSA in combination with CIS	Human Phase II clinical trial	MTX-HSA in combination with CIS displayed a 27% response rate in a Phase II study for the treatment of patients with advanced bladder cancer.
Protein-derived NP Robins et al.,[46] 2017	Albumin bound Nab-paclitaxel NP	Human Phase II clinical trial	The study group was patients with recurrent NMIBC who had previously been treated with intravesical BCG therapy. There was a recurrence-free survival rate of 18%, with 6 of the 28 patients remaining cancer free.
Silica-based NP Sweeney et al.,[48] 2017	MSN functionalised with a peptide (PEG-TRITC-Gd2O3-MSN)	Mice	(TRITC)–Gd2O3–MSN instilled into bladders of tumour-bearing mice enhanced T1 and T2-weighted MRI signals, improving the detection of the tumour limits.

Table 1 continued.

Nanostructure	Description	Subject	Comments
Silica-based NP Wei et al.,[50] 2017	PDA/doxorubicin-loaded MSN and peptide conjugation	Mice	Efficient anti-tumour effects of DOX-loaded NP by a xenograft tumour model *in vivo* was demonstrated.
Carbon-based materials Chen et al.,[55] 2012	SWNT were used as a delivery mechanism for THP. The SWNT were adapted with phospholipid-branched polyethylene glycol. After adaption, an SWNT-THP conjugate was constructed via a cleavable ester bond.	Rats	The study group was patients with superficial bladder cancer. SWNT containing THP showed an apoptosis rate of 96.85%. No side effects were observed.
Carbon-based materials Villela et al.,[57] 2014	rGO/CIS/DOXO on NIMBC	Rats	The tumour regression grades correlated with increased PTEN and decreased PI3K reactivities in the cancer+rGO+CIS+DOXO group.
Metallic NP Boucher et al.,[59] 2008	Ag	Rats	Intravesical administration of nanocrystalline Ag (1%) decreased urine histamine, bladder tumour necrosis factor-α, and mast cell activation without any toxic effects.
Metallic NP Hsieh et al.,[60] 2011	Au-EGCG	Mice	Au-EGCG inhibited tumour cell growing by means of cell apoptosis subcutaneously implanted with MBT-2 murine bladder tumour cells.
Metallic NP Zhang et al.,[61] 2013	β-glycerophosphate-magnetic NP of Fe_3O_4/CHI	Rats	These NP improved intravesical BCG retention time after the application of the magnetic field.
Metallic NP Chen et al.,[63] 2016	Au/antibody (EGFR)	Mice	Orthotopic bladder cancer model treated by using PTT exhibited a significant difference in tumour development.
Metallic NP Fávaro et al.,[64] 2017	Ag: Biogenic silver NP	Mice	In the treatment of chemically induced NIMBC by MNU, Ag NP 0.05 mg/mL exhibited 100% of tumoural regression (50% normal urothelium and 50% flat hyperplasia, which is a benign lesion).

Ag: silver; Au: gold; BCG: Bacillus Calmette–Guérin; BCG-CWS: BCG cell wall skeleton; CD: cluster of differentiation; CIS: cisplatin; CHI: chitosan; CWS-NP: cell wall skeleton-nanoparticle; DOTMA: N-(1-[2,3-dioleyloxy]propyl)-n,n,n-trimethylammonium chloride; DOX: doxorubicin; DPP: 1,2-dioleoyl-3-trimethylammonium propane/methoxypoly (ethyleneglycol); EGCG: (-)-epigallocatechin-3-gallate; EGFR: epidermal growth factor receptor; Fe: iron; HA: hyaluronan; HDAC: histone deacetylase; HT: hyperthermia; MBT-2: mouse bladder tumour cell line; MTX-HAS: methotrexate-albumin; MSN: mesoporous silica nanoparticles; Nab: nanoparticle albumin bound; NDAT: nano-diamino-tetrac (tetraiodothyroacetic acid); NDAT-CIS: nano-diamino-tetrac (tetraiodothyroacetic acid-cisplatin); NIMBC: non-muscle invasive bladder cancer; NP: nanoparticle; O: oxygen; PBS: painful bladder syndrome; PDA: polydopamine; PGON: poly(guanidinium oxanorbornene); PI3K: phosphatidylinositide 3-kinase; PLC: poly-ε-caprolactone; PLGA: poly(lactic-co-glycolic acid); PLK: polo-like kinase; PTEN: phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; PTT: photothermal therapy; rGO: reduced graphene oxide; SWNT: single-walled carbon nanotubes; THP: tetrahydropyranyl-adriamycin; TRITC: tetramethylrhodamine isothiocyanate.

These modified nanoparticles include gum arabic-coated radioactive, hyaluronic acid functionalised fluorescent, epigallocatechin-3-gallate, and antibody-coated silica nanoshells. To target bladder cancer, epidermal growth factor receptor, mucin 7, and cytokeratin 20 are commonly used.[22]

Photothermal therapy (green laser-532 nm) for targeting superficial bladder cancers using a green light laser in conjunction with GNP conjugated to antibody fragments (anti-epidermal growth factor receptor) resulted in the production of a thermal energy to kill urothelial carcinomas at very low energy levels, in both *in vitro* and *in vivo* mice models. In an orthotopic

bladder cancer model, animals treated by using photothermal therapy exhibited significant differences in tumour development.[63]

Biogenically synthesised silver nanoparticles suspensions were intravesically injected in 20 female mice (C57BL/6),[64] with NMIBC induced by administration of *N*-methyl-*N*-nitrosourea.[19] The urinary tract in the control animals did not show microscopically alterations. In contrast the *N*-methyl-*N*-nitrosourea group exhibited drastic histopathological alterations, such as urothelial carcinoma with invasion in the lamina propria and urothelial papillary carcinoma. For animals treated with N-methyl-N-nitrosourea and silver nanoparticles 0.05 mg/mL, the authors reported 100% tumour regression (50% normal urothelium and 50% flat hyperplasia, which is the beginning of the lesion) (Table 1).[64]

CONCLUSION

Nanotherapies are a promising approach for bladder cancer treatment due to their excellent results. The combination of nanomaterials with chemotherapeutic agents is able to provide a sustained and controlled drug delivery directly to the target site of application, increasing drug uptake by tumour cells and decreasing the side effects. This disruptive innovation must be seriously considered with regards to design safety, as this will permit important developments; however, more studies are required in this field.

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Acquired Male Urethral Diverticula: Diagnosis and Surgical Management

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Abstract

Background: A urethral diverticulum (UD) constitutes a localised saccular dilation that forms out of any point in the urethra's length, contiguous with the true urethral lumen through an orifice with a variable size neck. Disturbance of urine drainage from this outpouching leads to urinary stasis, recurrent urinary tract infections, lithiasis formation, an increase in UD size, urinary leakage or fistulas, incontinence, or even a palpable penoscrotal mass. UD occurs far more frequently in women and is very rare in men, with the incidence and prevalence in males remaining largely unknown.

Objective: The purpose of this paper is to present an updated review of acquired male UD, according to clinical presentation, diagnostic imaging findings, management, complications, and outcomes.

Material and Methods: Literature searches were conducted using Medline, Embase, and Cochrane databases in June 2015 to identify papers related to acquired male UD, concerning type, aetiology, presentation, radiologic and/or surgical intervention, and outcomes.

Discussion: The most common symptoms are obstructive lower urinary tract symptoms along with haematuria. Additionally, both congenital and acquired diverticula at the penoscrotal angle are frequent. Diagnosis alternates between physical examination and specific imaging, with individualised treatment now being standard practice varying with the location and size of the diverticulum. Besides conservative and observational follow-up, endoscopic and open surgical techniques are the selected definitive management options.

Conclusion: An acquired male UD is rare and must be considered in the differential diagnosis of suspicious penile and scrotal masses. If there is significant urinary stasis, recurrent urinary tract infections, or urethral calculi, a rigorous and thorough clinical examination followed by surgical correction is most often standard procedure, allowing for treatment of symptoms and aetiology simultaneously. Reconstructive urethral surgical corrections are very complex and require a specialised approach, often found only in high-volume surgical centres.

INTRODUCTION

The urethra is a tubular structure with a median length of approximately 17.5–20.0 cm. Its anterior segment stretches from the lower limit of the urogenital diaphragm down to the urethral meatus and can be further divided into bulbar urethra (surrounded by the bulb of the corpus spongiosum) and penile or pendulous urethra (surrounded by corpus spongiosum).[1,2] A urethral diverticulum (UD) is a condition in which a localised saccular of fusiform outpouching forms out of any point in the urethra's length. This saccular dilatation is contiguous with the true urethral lumen through a discrete orifice with a variable size neck. Inadequate urine drainage from this outpouching leads to urinary stasis, recurrent urinary tract infections, lithiasis formation, an increase in UD size, urinary leakage or fistulas, incontinence, or even a palpable penoscrotal mass.[3,4]

UD occurs far more frequently in women, most likely due to poor anatomical support of the urethra, complications from childbirth, or a more typical occurrence of periurethral abscesses.[5,6] UD are estimated to occur in 1–6% of women, presenting usually from the third to the fifth decade of life.[6] In men, it is a rare finding, and literature related to male UD generally involves case reports or small patient series with no estimated prevalence reported.[1,7]

According to Watts,[8] UD may be congenital or acquired in origin. Congenital UD are usually associated with congenital anterior urethral valves and aetiologic mechanisms remain to be ascertained: failed attempt of urethral duplication, failure of alignment between proximal and distal urethra, anomaly of the developing urethra resulting in excessive tissue growth and a permanent valve or flap mechanism, and a cystic dilation of periurethral glands.[9] These types of diverticula harbour all the layers of the urethral wall and are lined by epithelium. Acquired UD correspond to 67–90% of all male diverticula and is associated with an iatrogenic background, resulting in conditions such as obstructing urethral stricture, blunt trauma, and infection.[3] In children, imperforate anus is alsocommon following surgery.[3,10] These types of UD are covered by granulation tissue and their walls lack a true smooth muscle layer, only lined by a transitional epithelium and presenting a pseudodiverticulum image.[11] Congenital and acquired UD both share the same common feature: blind-ending outpouchings of the urethra.[12]

Acquired UD in males is a very uncommon and rare condition and the literature associated to it is scarce; as such, its incidence and prevalence remains unknown. It is mostly found at the penile urethra, especially at the penoscrotal angle.[13] Several factors have been described as responsible for UD development: strictures; recurrent urinary tract infections, including periurethral suppuration as a result of gonorrhoea, tuberculosis, or chronic urethritis infections; long-term or recurrent catheterisation; urethral or penile surgery; trauma; and erosion from surgical implants or from the use of penile clamps.[5,14] Inflammation of the periurethral glands with the formation of abscesses that burst into the urethral lumen has also been reported. Any of these risk factors should raise the clinician's suspicion for an acquired UD.

Possible explanations for male UD include:

- Increased urethral pressure from a urethral obstruction, with consequent outpouching of the urethral epithelium. Particularly in patients with a background of reconstructive procedures for hypospadias, urethral stricture, trauma, or incontinence.[15]
- Following anorectal malformation repair from a retained portion of the urethral fistula ballooning out as more urine is sequestered in the herniated structure.[16]
- In patients with indwelling urethral catheters: the constant pressure at the penoscrotal angle with chronic urethral ischaemia, urethral fibrosis, and scar formation.[17]

The purpose of this paper is to present an updated review of acquired male UD according to clinical presentation, diagnostic imaging findings, management, complications, and outcomes.

MATERIAL AND METHODS

A literature search was conducted using Medline, Embase, and Cochrane databases in June 2015 to identify papers related to acquired male UD concerning type, aetiology, presentation,

radiologic and/or surgical intervention, and outcomes. Publications not concerning humans were not considered. We identified original articles, review articles, and editorials addressing the subject. All articles published in the English language were selected for screening. The online electronic literature search involved unrestricted, fully explored Medical Subject Headings using terms related to secondary UD in adult men. Two independent reviewers selected all relevant articles and all duplicates were eliminated. The relevant articles were selected after reading the full text of the manuscripts and the eligibility criteria for inclusion was based on relevance concerning the subject. If there was any doubt concerning the eligibility of a study, abstracts and/or the full text were examined. Additional papers were identified from the reference lists of these articles.

CLINICAL PRESENTATION

Symptoms of UD vary dependent on the size, site, and degree of obstruction. Clinically, these patients may be completely asymptomatic. As expected, acquired UD patients present later than patients with congenital UD. The most common symptoms are obstructive lower urinary tract symptoms, postmicturition dribble, recurrent urinary tract infections, perineal pain, dysuria, urinary incontinence, with some cases of penile or perineal swelling, or even scrotal oedema.[5,12] Haematuria is also a common finding and a full workup on its aetiology should be carried out.[13]

DIAGNOSIS

In a paper by Allen et al.,[15] the most common location for both congenital and acquired diverticula is the penoscrotal angle, perhaps due to long-term urethral catheterisation. Large diverticulum can be diagnosed by palpation during clinical examination and the liquid content, if any, can be drained using this procedure (Figure 1).[12] A diverticulum of smaller dimension requires specific imaging to be identified and to efficiently decide on adequate management.[12]

Conventional contrast studies, including ascending urethrography and voiding cystourethrography, along with urethrosonography and cystourethroscopy, are recommended for an adequate diagnosis of UD (Figure 2). Additional imaging may be required if a distorted anatomy is present and to delineate a surgical strategy.[5,18]

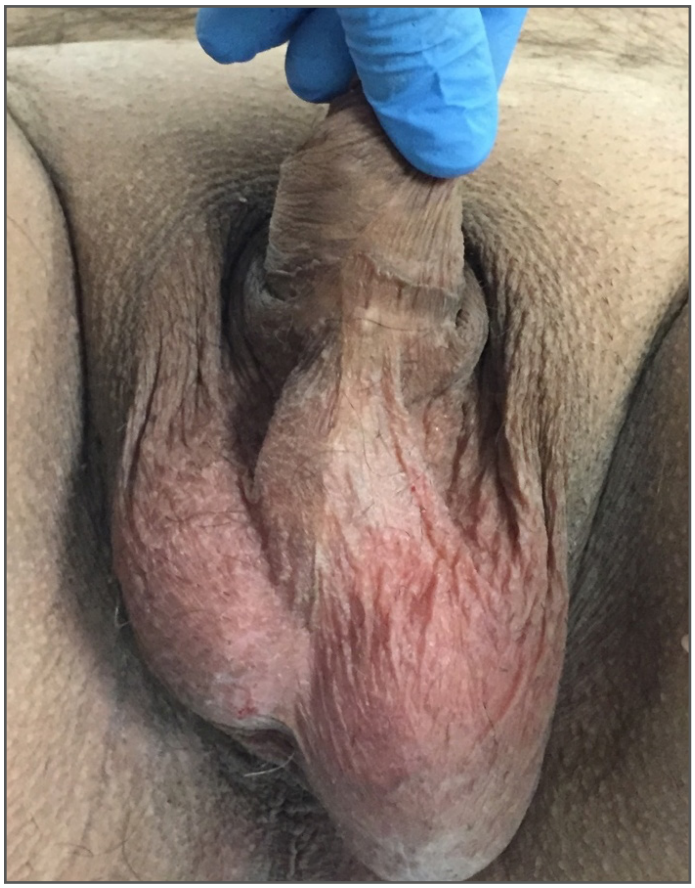

Figure 1: Enlarged urethral bulging mass corresponding to an anterior diverticulum.

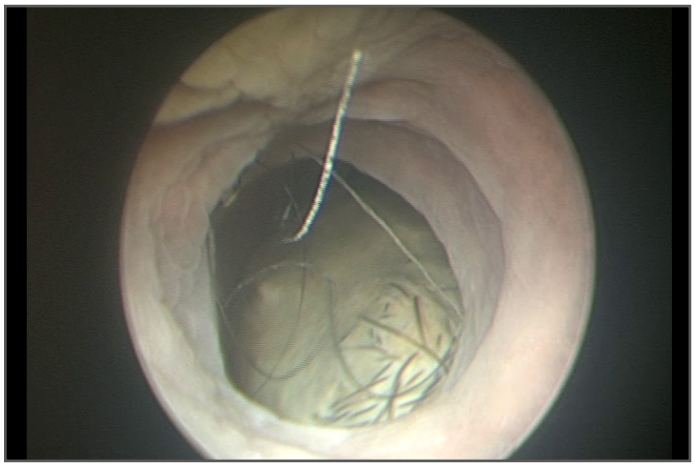

Figure 2: Urethral diverticulum with visible calculus on urethroscopy.

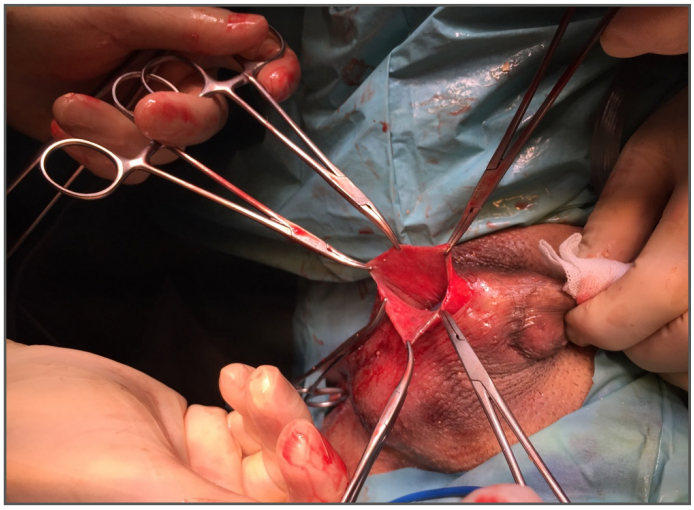

Figure 3: Open surgery for removal of a large anterior urethral diverticulum.

Using high-frequency linear probes and the intermittent introduction of normal saline solution to distend the urethra, the anterior urethra and perineal tract can be examined. The bulbar urethra should be scanned by placing the probe longitudinally on the ventral surface of the penis, or transperineally after having lifted the scrotum. Transversal scans can be used to explore focal lesions.[1]

Magnetic resonance imaging (MRI) is a sensitive and specific technique that has been proven effective at determining the size and extent of UD in women, but clinicians still lack experience when dealing with male urethra given the scarcity of these situations;[19] additionally, it is a costly and not easily accessible procedure, which precludes its use as a first-line examination.[20] Despite this, diagnosis and management of UD is greatly improved with this technique and cross-sectional imaging is increasingly being used in association with the former techniques; thus, this allows the clinician to clearly define the extent and location of the diverticulum, the integrity of the support structures, and to choose whether to perform an endoscopic or open surgical excision.[13]

MANAGEMENT AND OUTCOMES

Treatment should be individualised according to the location and size of the diverticulum, the presence of concomitant infection, and other pathologic findings that may need to be addressed. Small asymptomatic lesions may be monitored, particularly if the UD can be manually emptied. Some authors advocate a first-line approach with endoscopic incision of the diverticulum by transurethral unroofing if the integrity of the corpus spongiosum is intact and a good surrounding supportive tissue exists,[10,13,21] which is evidenced by the lack of a bulge in the penis or scrotum during micturition. Despite being a technically easier option, the rate of UD recurrence and urethrocutaneous fistula is higher than in open procedures.[3] Scar tissue formation and subsequent urethral stricture is also a possible outcome after endoscopic approach.[13]

An open procedure should be selected if an endoscopic approach is deemed to be unsuccessful, in the presence of recurrent urinary tract infections despite antibiotic therapy, or if there is an obstructive voiding or a stone in the UD (Figure 3).[3] Open management options include primary anastomosis after UD excision or substitution urethroplasty, restoring urethral continuity while providing a good vascular network and an adequate support structure. A flap or two-stage repair may be an option, both of which are the most risk-free techniques.[5] The risk of urethrocutaneous fistula with the possibility of additional surgical procedures (especially if a primary procedure was carried out) means that interposition of additional healthy tissue between the urethra and the diverticulum (e.g., dartos fascia) may be a good preventive measure.[5,21]

Cases of epididymo-orchitis following catheter removal have been reported.[3] Consequently, it is recommended that urethrography and prophylactic oral antibiotics are administered postoperatively until catheter removal in order to confirm success of the procedure.[2] If a patient is unsuitable for surgery (e.g., multiple urethral surgeries, extensive fibrosis from local radiation, or anatomical abnormalities) urinary diversion can be a suitable option.[3] It may also be appropriate in patients with neurogenic bladders for whom frequent urethral catheterisation is to be expected, compromising urethral healing or even increasing the risk of UD recurrence.[3]

In a paper from Parker et al.,[22] <100 cases of urethral carcinoma resulting from UD were reported. It occurs more often in women than in men, with a typical squamous or clear cell adenocarcinoma differentiation. Given this fact, freezing sections of the diverticular walls during its resection may be advisable.

CONCLUSION

A male acquired UD is a rare finding. It must be considered in the differential diagnosis of suspicious penile and scrotal masses, and if a large diverticulum is found. If there is significant urinary stasis, recurrent urinary tract infections, or urethral calculi, a rigorous and thorough clinical examination followed by surgical correction is most often standard procedure, allowing for treatment of symptoms and aetiology simultaneously. Reconstructive urethral surgical corrections are very complex, requiring a specialised approach, and are often found only in high-volume surgical centres. Other patients may be managed with urinary diversion only, rather than surgery.

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Personalised Management of Prostate Cancer

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Abstract

Despite recent advances, prostate cancer continues to be a leading cause of cancer-related death among men. While the standard management options of surgery, radiotherapy, and androgen deprivation therapy are well established, there are still significant unmet needs. For example, which patients would best be served by active surveillance at the time of diagnosis versus proceeding with definitive therapy is still not well understood. Additionally, more accurate means of monitoring patients' responses to therapy and remission statuses following therapy are needed. Since all patients with metastatic disease ultimately progress to castration-resistant prostate cancer, new treatment options for this population are also required. As in other areas of oncology, greater personalisation of care holds the potential for more effective treatment while also reducing the risk of adverse effects and morbidity. This review addresses three topics currently under investigation related to the personalised management of prostate cancer: the use of circulating tumour cells in both diagnosis and treatment at all stages of the disease, the introduction of poly(adenosine diphosphate-ribose) polymerase inhibitors for the treatment of castration-resistant prostate cancer, and the emerging role of genomic assays for risk stratification at the time of diagnosis.

INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men worldwide and the fifth leading cause of cancer-related deaths.[1] The majority of patients are diagnosed with localised disease, which is managed with radical prostatectomy (RP) or radiotherapy (RT). Despite high progression-free survival (PFS) rates, up to approximately 30% of patients treated with surgery[2] and 30–50% of those treated with RT[3] eventually experience disease recurrence.

The heterogeneous biology of prostate cancer has led to increased interest in personalised approaches to management of the disease. This narrative review focusses on three areas of active investigation: the use of circulating tumour cells (CTC) in diagnosis and monitoring of treatment response, the role of poly(adenosine diphosphateribose) polymerase (PARP) inhibitors, and the potential applicability of multigene assays to aid in risk stratification at diagnosis. The information detailed in this review was obtained via PubMed searches for the terms "prostate cancer", "circulating tumour cells", "PARP inhibitor", and "multigene assay".

CIRCULATING TUMOUR CELLS IN THE DIAGNOSIS AND MANAGEMENT OF PROSTATE CANCER

CTC are cancer cells shed from the primary tumour or from a metastatic focus into the circulation, and enumeration and analyses of CTC are being used in the diagnosis and management of various malignancies. Although the presence of these cells was recognised in the 19th century,[4] several technical challenges limited the feasibility of CTC use until the last decade. These include the relative rarity of CTC in the bloodstream, in part due to their short lifespan in this environment, as well as the presence of multiple subpopulations of CTC in the parent tumour.

Identification of Circulating Tumour Cells

The number of CTC present in patients with solid tumour malignancies is known to be low. Frequencies as low as 1 CTC per 7.5 mL of blood from patients with metastatic prostate cancer have been reported.[5] Thus, much of the work directed at improving the clinical applicability of CTC has aimed at improving the sensitivity of technologies for their detection. Several techniques have been developed to isolate CTC by exploiting their unique physical and immunologic properties.[6]

Immunoaffinity is one of the methods used to isolate CTC, based on cell-surface markers such as the epithelial cell adhesion molecule (EpCAM). Various devices have been developed utilising specialised beads, microposts (also known as CTC-chip), and *in vivo* wires or needles. CELLSEARCH® (Menarini Silicon Biosystems, Inc., Bologna, Italy) is a platform that was developed to identify breast, colon, and prostate cancer CTC using anti-EpCAM antibodies attached to ferrofluid nanoparticles. After the antibodies bind to the target cells, they are removed from solution using a magnet. The isolated cells are stained with 4',6-diamidino-2-phenylindole (DAPI) nuclear stain, as well as antibodies directed against cytokeratin (CK) and CD45. CTC are identified by their staining pattern as EpCAM-positive, DAPI-positive, CK-positive, and CD45-negative.

The microfluidics system CTC-chip uses a chamber with thousands of microposts embedded with antibodies to Ep-CAM. Cells passed through the CTC-chip can then be detected using immunofluorescence techniques. Stott et al.[7] isolated prostate cancer CTC using the CTC-chip, then flowed a rabbit antibody specific to prostate-specific antigen (PSA) through the chip, followed by a goat antibody that was fluorescently tagged to rabbit immunoglobulin G.

The above techniques are based on cell-surface markers and so their effectiveness is compromised by the heterogeneity of expression in a particular CTC population. Since EpCAM is a generic epithelial marker, systems based on this antigen have reduced sensitivity in the presence of other epithelial cells. In addition, cells have to be fixed for identification with the CELLSEARCH platform, so live CTC cannot be isolated by this method.

Several other techniques for CTC isolation are based on differences in size and deformability. Generally, CTC are larger and more rigid than benign cells; this has led to approaches using filters such as membranes or adjustable cell traps.[8] These platforms allow recovery of live CTC but still have limitations of sensitivity and specificity, and require staining to confirm identification.

Monitoring of Disease Status

Prostate cancer CTC have been used in a variety of settings, from localised to metastatic disease. Some of the studies are summarised here.

Localised Disease

Puche-Sanz et al.[9] demonstrated that CTC could be detected in prostate cancer patients at the time of diagnosis. CTC were isolated from 86 patients with clinical suspicion of prostate cancer who met the criteria for prostate biopsy (based on PSA >10 ng/mL or PSA 4–10 ng/mL with a free/total PSA ratio <0.2). The Carcinoma Cell Enrichment and Detection Kit (Miltenyi Biotec, Bergisch Gladbach, Germany) was used, which involves magnetic beads labelled with a multi-CK-specific antibody. In this population with a low burden of disease, the rate of CTC detection was 18.6%.

Kuske et al.[10] combined the CELLSEARCH platform with two other techniques to enhance the sensitivity and specificity. The CellCollector® (GILUPI, Potsdam, Germany) uses a sterile stainless steel medical wire coated with antibodies to EpCAM, enabling collection of CTC *in vivo*.[11] A third EpCAM-independent assay, EPISPOT, is an adapted enzyme-linked immunospot assay.[12] By combining these approaches, the detection rate improved from 37.0% to 59.0% for the individual assays, and to 81.3% for the combined approach.

Metastatic Hormone-Sensitive Prostate Cancer

Currently, patients who undergo curative treatment with either surgery or radiation are monitored for recurrence via serum PSA level, typically in the setting of androgen deprivation therapy. CTC have been investigated as additional biomarkers of response. Roviello et al.[13] investigated the correlation of CTC detectability with clinical recurrence in patients with hormone-sensitive disease who had received curative treatment. Using the CELLSEARCH assay, CTC were detected in 14 of the 42 (33.3%) patients enrolled. This group was found to have a significantly higher mean PSA level and was significantly more likely to have bone metastases compared to the CTC-undetectable group. In addition, Josefsson et al.[14] collected CTC from 46 of the 53 (87%) patients with metastatic hormone-sensitive prostate cancer who were assayed with the CELLSEARCH platform. The presence of CTC was found to be associated with shorter PFS. In particular, expression of epidermal growth factor receptor on CTC demonstrated significant negative prognostic value, with a PFS of 5 months versus 11 months for those in whom epidermal growth factor receptor was not detected.

Metastatic Castration-Resistant Prostate Cancer

Much interest has focussed on the utility of CTC as leading indicators of the emergence of resistance to androgen blockade, or as prognostic markers in the management of patients already known to have castration-resistant prostate cancer (CRPC). An important study was conducted by de Bono et al.[15] in which peripheral blood from 231 patients with CRPC was assayed for CTC, both before and after initiating each new line of therapy. Patients were divided into groups of favourable or unfavourable CTC counts, based on whether <5 or ≥5 CTC were collected in a 7.5 mL sample. Using this method, median overall survival was found to be significantly longer in the favourable group (20.7 months) versus the unfavourable group (9.5 months). CTC count was demonstrated to be more accurate in predicting overall survival than the alternative measure of PSA decrease.

One mechanism for the development of castration resistance is the amplification of the androgen receptor gene (*AR*). Podolak et al.[16] collected both peripheral blood CTC and biopsy tissue from a group of 25 patients with metastatic CRPC and measured *AR* amplification in the samples. Twenty-four (96%) of the patients demonstrated concordance of *AR* status, an encouraging result that suggests a CTC assay could ultimately replace biopsy in some cases.

Another key mechanism of castration resistance is the development of the abnormally spliced androgen receptor AR-V7. Antonarakis et al.[17] studied a population of 202 patients with metastatic CRPC being treated with abiraterone or enzalutamide, looking at three separate subgroups: CTC-negative, CTC-positive/AR-V7-negative, and CTC-positive/AR-V7-positive. Clinical and radiographic PFS, the primary endpoint of the study, was significantly different, measuring 13.9 months for the CTC-negative group versus 7.7 months for the CTC-positive/AR-V7-negative group and 3.1 months for the CTC-positive/AR-V7-positive group. These results suggest that the presence of CTC is itself a poor prognostic factor, with the presence of AR-V7-positive CTC having a particularly negative implication. The aforementioned investigations demonstrate the increasing role and applicability of CTC in the management of prostate cancer, potentially from the time of diagnosis and continuing through advanced disease.

ROLE OF POLY(ADENOSINE DIPHOSPHATE-RIBOSE) POLYMERASE INHIBITORS

Significant effort has been directed towards personalised management of the population of patients with metastatic CRPC, an entity that exhibits considerable genetic heterogeneity. Approximately 90% of these cancers contain actionable mutations. Robinson et al.[18] reported an analysis of 150 cases that demonstrated that 22.7% of patients had alterations in DNA repair genes. The observation that some cases of CRPC contained mutations in *BRCA1*, *BRCA2*, and *ATM* suggested that these cancers might be sensitive to treatment with inhibitors of backup DNA repair pathways, an approach referred to as synthetic lethality. The development of PARP inhibitors facilitated this new approach to management of CRPC.

Castration-Resistant Prostate Cancer with Germline DNA Repair Mutations

Initial studies of *BRCA1* and *BRCA2*-mutated prostate cancer focussed on germline mutations, which were found to be associated with a higher Gleason score (range: 2–10; higher score represents more aggressive disease), T stage, likelihood of nodal involvement, and likelihood of metastatic disease at diagnosis, as compared with wild-type cancers.[19] The development of PARP inhibitors heralded a novel targeted approach, with a proof-of-concept basket trial of *BRCA1* and *BRCA2*-mutated cancers. Fong et al.[20] treated a cohort containing some patients with germline *BRCA1* and *BRCA2*-mutated ovary, breast, and prostate cancer with the PARP inhibitor olaparib. Only mutation carriers responded and less toxicity was observed than that seen with standard chemotherapy options. Further studies targeting germline *BRCA2*-mutated prostate cancer alone also demonstrated a response to olaparib.[21]

Castration-Resistant Prostate Cancer with Sporadic DNA Repair Mutations

With the activity of PARP inhibitors in germline-mutated CRPC established, interest developed regarding their applicability to CRPC with sporadic mutations of DNA repair genes. A pivotal study by Mateo et al.[22] (the TOPARP-A trial) examined the use of olaparib in a cohort of patients with CRPC of unknown DNA repair mutation status. Subjects underwent a prospective series of biomarker studies, including whole-genome sequencing and transcriptome analysis; CTC analysis was performed using the CELLSEARCH platform. Of the 49 patients evaluated, 16 had an objective response (33% response rate), while 14 patients (29% response rate) showed a reduction in CTC count. Next-generation sequencing revealed that 16 patients had mutations in DNA repair genes (referred to as biomarker-positive), including 7 patients with alterations of *BRCA2*. Notably, patterns of response were different between the groups, with significantly higher response rates in biomarker-positive patients. Eighty-eight percent of patients with DNA repair mutations responded to olaparib, whereas only 6% of the biomarker-negative patients responded. Additionally, olaparib was generally well tolerated, with the most common Grade 3–4 adverse effect being anaemia, which 20% of patients presented with.

Inducing 'BRCAness'

The degree to which a given cancer is deficient in homologous recombination, such that it is sensitive to treatment with PARP inhibitors, has been referred to as 'BRCAness'. Only a minority of CRPC contain DNA repair mutations and ongoing studies are investigating whether the quality of BRCAness can be induced therapeutically. Significantly, AR signalling pathways have been demonstrated to regulate the expression of DNA repair genes;[23] additionally, PARP-1 has been found to promote the activity of AR.[24]

Based on preclinical work using the antiandrogen enzalutamide, Li et al.[25] hypothesised that blocking this pathway in CRPC cells would enhance their BRCAness and render them more susceptible to PARP inhibition. A lead-in strategy was used in which prostate cancer cells from the cell lines VCaP and LNCaP (American Type Culture Collection, Manassas, Virginia, USA) and CWR22Rv1 (Memorial Sloan Kettering Cancer Center, New York City, New York, USA) were treated with enzalutamide for 24 hours, then with a combination of enzalutamide and olaparib for 48 hours. These were compared with cells

treated with enzalutamide and olaparib concomitantly, and the lead-in strategy was found to be more effective at impairing cell growth.

GENOMIC TESTING FOR RISK STRATIFICATION

Contemporary treatment options for newly diagnosed localised prostate cancer include surgery (RP with or without pelvic lymph node dissection), radiation (external beam RT or brachytherapy) with androgen deprivation therapy, or active surveillance.[26] The choice among these options is guided by the degree of risk associated with the individual patient's disease, an assessment that is largely based on the aggressiveness of cells in the prostate biopsy (reported as Gleason score). However, the accuracy of biopsy is limited due to tumour heterogeneity and sampling errors. Hence, a growing area of interest in personalised prostate cancer care relates to predictive models to improve risk stratification. Ongoing efforts are focussed on the development and use of multigene assays to better characterise prostate cancer, starting at the time of diagnosis, an approach somewhat analogous to that used currently in the management of breast cancer.[27]

Genomic Prostate Score Assay

Klein et al.[28] developed a 17-gene assay called the genomic prostate score (GPS) to risk-stratify newly diagnosed localised prostate cancer using a multistep methodology. First, 441 prostatectomy samples were analysed to help generate candidate genes for the multigene assay. Second, a validation study was conducted comprising 167 patients who initially had a biopsy revealing prostate cancer and then underwent prostatectomy. In total, 732 genes were analysed, of which 288 were found to be predictive of recurrence and 198 were predictive of aggressive disease. Seventeen genes (12 genes associated with prostate cancer aggressiveness and 5 reference genes) were included in the finalised assay, after which the third component (prospective validation study) was conducted, which included 395 patients, all of whom were candidates for surveillance but elected to undergo prostatectomy within 6 months of the biopsy. A higher GPS value (scale: 0–100) was found to be associated with poorer clinical outcome when adjusted for Cancer of the Prostate Risk Assessment (CAPRA) score. Specifically, each 20-point increase in GPS was predictive of a 2.3-fold increased risk of high-grade disease at prostatectomy and was also associated with a 1.9-fold increased risk of non-organ-confined disease. A cut-off GPS value was not suggested.

A follow-up study by Cullen et al.[29] validated the GPS retrospectively in a group of 431 patients diagnosed with very low-to-intermediate-risk prostate cancer. Of this cohort of patients, 20% were African American. GPS was found to be predictive of outcome, including time to biochemical recurrence and time to metastasis, and median GPS was the same (30.3) for both African American and Caucasian patients.

Stratification of Patients with Intermediate-Risk Disease

Sinnott et al.[30] noted that the grading of prostate biopsy involves some degree of interobserver variability, and many patients are diagnosed with Gleason score 7 (intermediate-risk) disease. This group of patients is heterogeneous, with a wide range of prognoses, and traditionally they have been risk-stratified according to Gleason score 3+4 versus 4+3 disease (where the first score indicates the dominant histologic pattern present and the second score indicates the non-dominant histologic pattern). To better characterise this particular group, Sinnott et al.[30] developed a 30-gene signature specifically for use in patients with Gleason score 7 disease. Whole-transcriptome gene expression profiling was performed on 113 prostate cancer specimens (either from RP or transurethral resection of the prostate) from patients who died of the disease or developed distant metastases. Subsequently, another 291 samples were analysed from patients with indolent disease who did not develop metastases and died of non-prostate cancer-related causes. All patients in both groups were classified as having intermediate-risk Gleason score 7 tumours. A signature containing 157 genes was developed using these gene expression profiles, which was narrowed to 30 genes. The score generated ranged 0–1, with lower scores more similar to Gleason score ≤6 disease, while higher scores were more similar to Gleason score ≥8.

When compared to Gleason score alone, the 30-gene score was found to be more predictive of aggressive disease. The score was a stronger predictor of lethality than Gleason score 3+4 or 4+3 status, although this difference was not statistically significant.

Methylation-Based Assay

Epigenetic factors, such as methylation, have been recognised as playing a role in carcinogenesis. Vasiljević et al.[31] analysed 13 genes in 367 men with localised prostate cancer, specifically looking at the methylation status. Twelve of the 13 genes analysed were associated with prostate cancer-related death and the hazard ratios increased with the degree of methylation. Subsequently, the same group developed a methylation score for risk stratification of low-to-intermediate-risk prostate cancer.[32] Six genes from the previous set of 13 were selected for inclusion in the methylation score. Transurethral resection of the prostate samples from 385 patients with low-to-intermediate-risk CAPRA scores were assayed to determine the methylation statuses. The methylation score was found to be a stronger predictor of prostate cancer-related death than CAPRA score and the difference was statistically significant, with hazard ratios of 2.72 and 1.62, respectively.

CONCLUSION

Prostate cancer is a common malignancy and a major contributor to the global burden of cancer-related morbidity and death. One of the striking features of the disease is its heterogeneity in presentation and clinical course, with some patients having indolent disease and minimal symptom burden while others experience highly aggressive disease. This review has summarised some of the efforts and data collected regarding greater personalisation of care for patients with prostate cancer, with the goal of avoiding overtreatment of lower-risk patients while targeting higher-risk patients for more appropriate management.

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Urethral Reconstruction Using Cell-Based Tissue Engineering Approaches

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Abstract

Urethral reconstruction for complex conditions remains a challenge because of the unsatisfactory long-term results and problems associated with the harvesting of adequate replacement tissues. Tissue engineered substitutes, either scaffolds alone or in combination with cells, can overcome some of the aforementioned problems. Currently, such tissue engineered substitutes have been gaining popularity, as evidenced by >80 published preclinical and 20 clinical studies. This review summarises the currently available literature on the cell-based tissue engineered substitutes (11 studies) for urethral reconstruction. Clinical translational challenges and future directions are also discussed.

INTRODUCTION

Normal urethral function can be severely impaired by congenital or a variety of acquired urethral conditions, such as hypospadias, strictures, fistulas, trauma, and cancer. Numerous reconstructive techniques have been developed to restore urethral function in such conditions. Despite this progress, reconstruction for addressing strictures and hypospadias still poses problems for urologists. Availability of adequate replacement for long urethral defects or the poor quality of the urethral plate remains a challenge. Reconstruction in such cases requires the use of additional tissue, such as local genital tissue flaps from preputial,[1] penile,[2] and scrotal skin,[3] or testicular tunica vaginalis,[4] or extragenital tissue grafts from skin,[5] buccal mucosa,[2] lingual tissue,[6] or colonic mucosa.[7] However, these techniques are not effective for long or complex strictures, and long-term follow-ups have demonstrated significant complications and decreased quality of life.[2] The major complications at the operation site include recurrence of stricture and fistula formation.[2,4,6,7] Complications also occur at the donor sites, such as difficulty in opening the mouth,[8] numbness,[8,9] discomfort,[9] nerve damage,[10] bleeding, and haematoma.[11] Also, donor tissue is limited for cases of panurethral strictures or recurring strictures, where tissues were harvested previously. Tissue engineering (TE) may overcome some of the aforementioned problems. Efficacious *in vitro*-engineered urethral tissue and off-the-shelf substitutes will represent a significant step in advancing urethral reconstructive surgery. Currently, there

are >80 published preclinical and 20 clinical studies for urethral TE substitutes.[12] In this review, we have evaluated currently available clinical studies regarding the potential of TE in urethral reconstruction; in particular, those describing the use of cells alone and in combination with scaffolds in humans. Translational challenges with such products and the possible future developments in this field are also discussed.

CELL-BASED TISSUE ENGINEERING OF THE URETHRA

TE aims to replace damaged tissues and organs and restore function by combining the fields of cell biology, materials science, and engineering.[1-4] Two strategies are employed in urethral TE: the first strategy is scaffold-based, in which natural or synthetic materials are used as grafts and urethral regeneration depends on the body's ability to heal; the second strategy is cell-based, in which urethral substitutes are engineered *in vitro* by cells alone or by combining cells with natural and/or synthetic scaffolds. An overview of urethral TE options is described extensively in the literature.[12-16]

Reconstructing urethras with various acellular natural and synthetic materials has been found to be safe and effective in animals.[12] Clinically, naturally derived off-the-shelf materials, such as small intestinal submucosa, bladder acellular mucosa, acellular dermis, and urethral acellular matrix were found to be safe, and demonstrated success rates of >75% in the majority of cases.[12,17] Failures were common in patients with longer strictures (>4 cm),[18,19] in those with penile or penile-bulbar strictures,[20] and in those with previous urethroplasty (unhealthy urethral bed, unsatisfactory vascularity).[21]

Table 1: Cell-based tissue engineered substitutes used in urethral reconstruction.

Author	Cells	Scaffold	Number of patients	Patient age (years)	Disease type	Technique	Follow-up (months)	Success rate
Romagnoli et al.,[22] 1990	Autologous UC	N/A	2	2–13	Hypospadias	Patch	6–18	2/2 (100%)
Romagnoli et al.,[23] 1993	Autologous UC	N/A	8	1.5–14.0	Hypospadias	Tube	24	7/8 (87.5%)
Fossum et al.,[24,25] 2007, 2012	Autologous UC from bladder washings	ADM	6	1.0–3.7	Stricture	Patch	35–103	5/6 (83%)
Bhargava et al.,[26] 2008	Autologous OEC/OF	ADM	5	36–66	Stricture	Patch	32–37 (mean: 33.6)	3/5 (60%)
Osman et al.,[27] 2014	Autologous OEC/OF	ADM	5	36–66	Stricture	Patch	110–115 (mean: 112)	3/5 (60%)
Raya-Rivera et al.,[28] 2011	Autologous BUC/BSMC	PGA/ PLGA	5	10–14	Stricture	Tube	36–76 (mean: 64.2)	4/5 (80%)
Barbagli et al.,[29] 2013	Autologous OEC	Collagen matrix	12	31–75	Stricture	Patch	10 months (range: 4–21 months)	11/12 (92%)
Beier et al.,[30] 2014	Autologous OEC	Collagen matrix	8	24–70	Stricture	Patch	3–18 (mean: 9.3)	8/10 (80%)
Ram-Liebig et al.,[31] 2015	Autologous OEC	Collagen matrix	17	24–76	Stricture	Patch	13–22	17/21 (81%)
Ram-Liebig et al.,[32] 2017	Autologous OEC	Collagen matrix	99	Data unavailable	Stricture	Patch	24	58/99 (58.5%)

ADM: acellular dermal matrix; BSMC: bladder smooth muscle cell; BUC: bladder urothelial cells; N/A: not applicable; OEC: oral epithelial cells; OF: oral fibroblast; PGA: polyglycolic acid; PLGA: poly(lactic-co-glycolic acid); UC: urothelial cells.

Cell-based TE substitutes overcome the limitations of acellular grafts by lengthening the distance over which regeneration occurs. Various cell and scaffold combinations were evaluated in animals with good success.[12,16] A meta-analysis of cell-based TE substitutes for urethral reconstruction in animals revealed that these grafts were 5.7-times better than unseeded grafts.[16] In another meta-analysis, cells significantly reduced the probability of strictures, stenosis, fistulas, and infections independent of the scaffold type.[12]

Despite multiple animal studies, only a few clinical studies of cell-based TE substitutes for urethral reconstruction in hypospadias and stricture have been published (11 studies, Table 1). PubMed and Google Scholar were queried for synonyms of TE (e.g., regenerative medicine and cells) and synonyms of urethral reconstruction (e.g., urethral repair and urethroplasty) to identify these clinical studies.

Romagnoli et al.[22] constructed neourethras in two posterior hypospadias patients with autologous stratified urethral epithelial sheets. In one patient this cell sheet was grafted onto the tissue bed, which had been exposed by incising the penile ventral surface. The neourethra, which exhibited organised stratified epithelium 10 days post-surgery, was tubularised and linked to the meatus after 6 months. The patient voided normally; however, fistulas developed on the ventral surface of the neourethra and at the junction of the neourethra and the meatus, which were surgically managed. At 1 year, normal urethral mucosa with stratified squamous epithelium was observed. In the second patient, the new urethra was tubularised and immediately connected to the meatus after 10 days. Fistulas developed at the junction of the new urethra and the original meatus. Stenosis at the coronal sulcus of the glans was also observed. Fistulas and stenosis were managed by surgery and dilation, respectively. Follow-up after 6 months demonstrated normal urinary and erectile functions and no stricture or fistulas.

Romagnoli et al.[23] modified their two-stage procedure into a one-stage procedure by directly implanting tubular autologous epithelial sheets in eight severe proximal hypospadias patients. The tubularised grafts were inserted into the subcutaneous tunnel prepared by dissection of the urethral meatus up to the fossa navicularis of the glans. The patients were followed for up to 2 years. Endoscopy was performed in all patients and biopsies were taken from four patients. One patient developed a fistula within 20 days. All patients exhibited stenosis at the coronal sulcus of the glans, which was managed by dilation. The mucosa was smooth with stratified epithelium.

Fossum et al.[24] used autologous urothelial cell-seeded acellular dermis in six males with severe scrotal or perineal hypospadias and pronounced chordee. Urothelial cells were harvested from bladder washes during Stage 1 of penile straightening. In Stage 2, TE graft was implanted in an onlay fashion with the cells facing the lumen. Cosmetic appearance, voiding function, urinary flow, urethroscopy, and histopathology were assessed for 3.0–5.5 years. Cosmetic appearance was considered good in all cases. The meatus had an adequate opening at or near the glans in all cases. All six males voided through their neourethras without straining and had no residual urine. Five patients voided in a standing position and presented bell-shaped flow curves. Restricture occurred at 12 months in one patient, which was managed by urethrotomy. Another developed a proximal anastomosis obstruction, which was managed with stenting. Two males developed fistulas, which were surgically corrected. All patients had a wide neourethra with smooth mucosa. Mucosal lining with urothelial cells were seen in three cases. Further long-term follow-up (6–8 years) showed that all six patients still had good cosmetic appearance, good voiding function, and straight artificial erections, with ingrowth of urothelium or squamous epithelium on the transplanted site.[25]

Bhargava et al.[26] reported the 3-year clinical results of TE urethroplasty for complex lichen sclerosis strictures. The TE graft with stratified epithelium was constructed with autologous oral epithelial cells and fibroblasts seeded onto acellular dermis. Both two-stage (n=3) and one-stage (n=1) procedures were performed. Visual examination and endoscopy was performed at follow-up. Of the two-stage patients, one patient underwent a complete graft excision due to fibrosis with chordee at 8 months, the second underwent a proximal graft excision due to hyperproliferation at 9 months, and the

third had sub-meatal stenosis that required dilation. The excised parts were substituted with oral mucosa. Both the one-stage patients developed stricture at the bulbar anastomotic site within 9 months; these were managed with urethrotomy. Osman et al.[27] reported the 9-year clinical results in these patients. Three patients continue to use intermittent self-dilation. All patients had a patent and normal urethra.

Raya-Rivera et al.[28] reported the effectiveness of tubularised TE urethras in five boys. Three of the boys presented with a complete posterior stricture, and two had previous failed posterior urethroplasty. Autologous muscle cells and urothelial cells were isolated from the bladder biopsy and expanded. The muscle cells were seeded on the outer surface and epithelial cells on the inner surface of tubularised polyglycolic meshes coated with poly(lactic-*co*-glycolic acid). These tubes were surgically implanted after stricture excision. The boys were followed for up to 6 years. Voiding function, urinary flow, urethroscopy, urethrogram, urethral biopsies, and questionnaire outcomes were assessed. All patients voided normally without dysuria, straining, or dribbling. None developed strictures or fistulas. All patients maintained wide urethral calibres. Neourethral histologic characteristics were similar to native urethra at 3 months and had no aberrant changes over time. One patient exhibited narrowing at the proximal graft anastomotic site that required incision.

MukoCell® (Urotiss Europe GmbH, Dortmund, Germany), an autologous cell transplant that uses oral epithelial cells in a collagen matrix, is a commercial TE graft available to German patients. The exact cell culture protocol and composition of the scaffold is unknown. One study assessed twelve patients with idiopathic uncomplicated bulbar urethral stricture who were treated with MukoCell. At a mean follow-up of 10 months, stricture reoccurred in one patient.[29] Ten patients with bulbar strictures were treated with Mukocell. At a mean follow-up of 9.3 months, strictures reoccurred in two patients.[30] Twenty-one patients with bulbar stricture (n=18) and proximal penile and bulbar stricture (n=3) were treated with MukoCell by a ventral onlay procedure.[31] Seventeen of these patients had some previous instrumentation. The median follow-up was 18 months. Seventeen patients were stricture free and urethrography showed a wide and patent urethra. The mean maximum peak flow increased from preoperative 9.9 mL/s to postoperative 30.0 mL/s. Restricture occurred by 11 months following urethroplasty. In one of these patients, the restricture occurred outside of the transplanted graft area. The failed procedures were treated successfully using either urethrotomy, dilatation, or meatoplasty.

Ram-Liebig et al.[32] recently published the 2-year safety and efficacy results of MukoCell for urethral strictures of various aetiology, location, and severity in a multicentre prospective observational trial. The urethroplasty was performed in eight German centres with various levels of experience. A total of 99 patients were included in this study. Except for one, all of the patients had multiple previously failed surgical interventions. Statistical analysis was also performed to identify risk factors for stricture recurrence. The success rate, defined as the absence of stricture recurrence, was 67.3% at 12 months and 58.2% at 24 months. The success rate was dependent upon surgeon skill and experience. The success rate varied between 85.7% in the case of high experience and 0.0% in the case of low experience. Timing of catheter removal and number of prior surgeries were identified as independent risk factors for stricture recurrence. Patients with catheter removal ≥28 days postsurgery had the highest risk of stricture recurrence, as did patients with four or more prior treatments.

The authors have also used TE to treat a single case of lichen sclerosis stricture in a 45-year-old with previous failed urethroplasty. Rangadore Memorial Hospital Ethics Committee, Bangalore, India, approved this study. A urethrogram showing stricturing in the anterior urethra can be seen in Figure 1A. Autologous oral epithelial cells were seeded onto denuded amniotic membrane mounted on a polypropylene mesh. This TE graft was monitored daily to examine cell morphology, proliferation, and sterility. Once the cells were confluent and found to be free of microbial and mycoplasma contamination, it was ready for transplantation. The fibrosed urethra was exposed ventrally until the healthy urethral tissue was reached proximally. After haemostasis, the TE graft was applied with cells facing the raw area and fixed at edges to the exposed corpus spongiosum (Figure 2A and 2B).

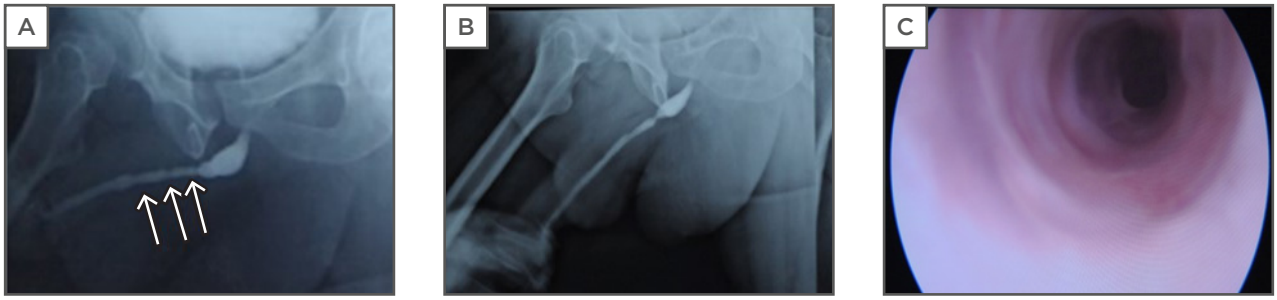

Figure 1: A) Urethrogram showing the narrowing (arrows) in the anterior urethra; B) urethrogram after 2 years showing the narrowing at anastomotic area; C) cystoscopy of the reconstructed urethra showing smooth and patent lumen with narrowing at the anastomotic site.

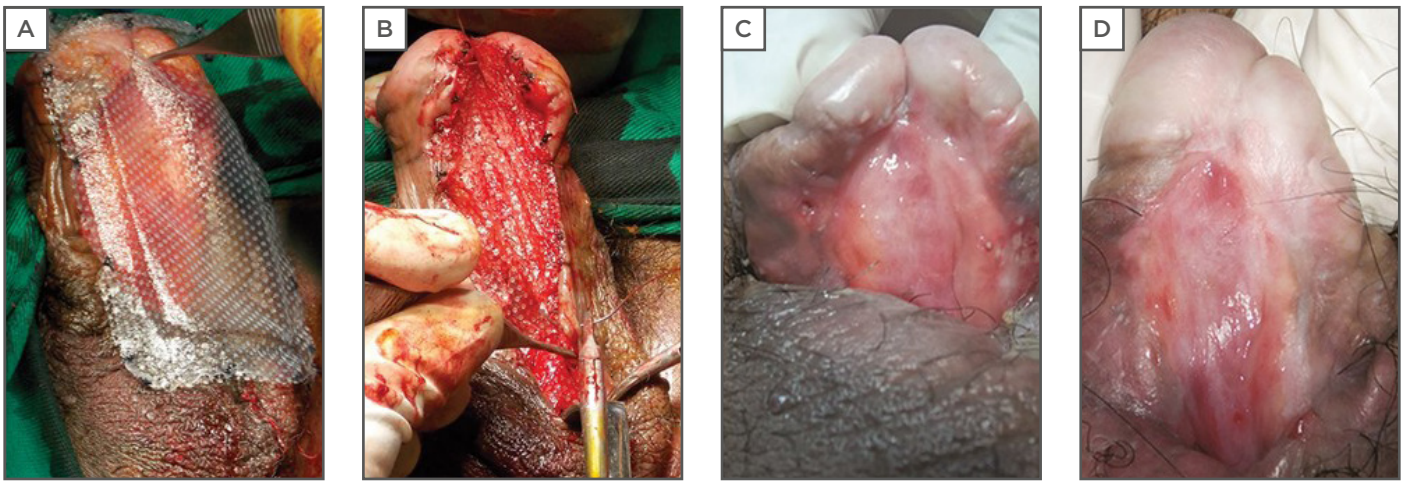

Figure 2: A) Placement of tissue-engineered graft on the excised area of the urethra; B) tissue-engineered graft affixed to the edges with sutures; C) healing of urethra 87 days after tissue-engineered graft; D) healing of urethra 193 days after tissue-engineered graft.

A catheter was inserted for voiding of urine via a proximal urethrostomy. The graft area was covered with a sterile dressing, which was removed after 2 days; the catheter and mesh were removed 4 days later. The grafted area was observed periodically for a period of 6.5 months to assess healing and epithelialisation. The graft area healed well, with complete re-epithelialisation (Figure 2C and 2D), and was elastic. No adverse reaction to the graft was observed. A biopsy taken from the healed area confirmed the presence of stratified epithelium. The urethra was then tubularised and the penis reconstructed. The patient was able to void normally without any pain. After 1 year, cystoscopy revealed smooth and continuous urethral mucosa (Figure 1C) with narrowing at the anastomotic site. A urethrogram at 2 years showed that the repaired urethra was still patent but with narrowing at the anastomotic site (Figure 1B).

All of the above studies demonstrate the feasibility and efficacy of using TE-based approaches for the treatment of urethral disease. Nonetheless, significant challenges remain.

TRANSLATIONAL CHALLENGES

Only a few TE products have been used clinically despite a plethora of preclinical studies suggesting that multiple challenges hamper the transition of TE products from bench-to-bedside. Some of these challenges include appropriate preclinical or clinical studies, regulations, cost, patient population, manufacturing facility, variability, off-the-shelf availability, surgical techniques, among others.

One major translational challenge is that the level of evidence from preclinical studies is low-to-moderate. The efficacy of TE products is evaluated in healthy animals that do not replicate the pathophysiology of urethral strictures and hypospadias. The graft uptake and the healing process in the normal urethral bed would be completely different from the diseased urethra. In such healthy animals, TE products might be more efficacious because of the presence of a vascularised healthy urethral bed. Furthermore, in many animal studies, unseeded scaffolds were considered as controls, not sham or standard treatment.[12,16] Susceptibility to publication bias may have also lead to overestimation of the treatment effect in preclinical studies. Most of the clinical studies have treated only a few patients, and hence a high level of evidence is not possible.

To ensure patient safety, quality, and efficacy, there are multiple regulatory oversights for TE therapies at all stages, starting from *in vitro* studies all the way to commercialisation. Unfortunately, regulatory pathways vary in different countries. The regulatory pathways are sometimes not able to keep up with the rapid progress made in TE, and approval processes are time-consuming and expensive. In other instances, TE are regulated by procedures established for conventional pharmaceutical products and are often inappropriate.

The cost of TE when compared to autologous grafts is very high. Currently, oral mucosa successfully repairs simple urethral strictures and hypospadias, so justifying the high cost in such cases is difficult. Hence, TE grafts may be required only in cases of extensive strictures or hypospadias, or in recurrent cases with previously failed graft urethroplasties. However, the complication and failure rates of the TE grafts in such cases could be expected to be high too, putting TE in a difficult position to prove itself. Additionally, the efficacy of the TE grafts can only be established in prospective, multicentred, randomised studies with appropriate control groups. This would be difficult, as the TE are developed for urethral conditions where current treatment is not satisfactory. Also, conducting such studies is expensive and time-consuming.

Unlike drugs and biologics, which have distinct reproducible properties, cells vary depending on the patient, further hampering translation of cell-based therapies. In addition, the patient's own genetic makeup can also influence many aspects, including, for example, the healing milieu. This issue may be even more relevant in patients with urethral strictures secondary to lichen sclerosis because it may be a genetic issue.

Another limiting factor is the long time required for the preparation of cell-based TE grafts and, at present, it is not suitable as an off-the-shelf product.

Furthermore, an important challenge is the TE graft placement technique used. Clinically, reconstructive surgeons have a variety of techniques that may be used according to factors such as aetiology, stricture position, and length. TE grafts should be demonstrated to be efficacious in all surgical techniques.

FUTURE DIRECTIONS

Robust assessment and evidence of successful TE grafts in animal models is crucial and mandatory before clinical testing. Currently, a few animal models are available for urethral diseases, but they do not fully recreate the complexity and compromised vascularity.[33-35] Hence, the development of validated animal models that reproduce these aspects faithfully is critical, and studies in these models with proper experimental design parameters are necessary. Furthermore, such animal models are ideal opportunities for research concerning the pathogenesis and molecular biology of urethral diseases.

Additionally, more basic studies are required to elucidate the molecular mechanisms of urethral stricture, which can lead to the development of better TE techniques that can counteract the stricture. For example, in a fibrosed urethra the expression of connective tissue growth factor is high.[36] Hence, TE approaches that can downregulate the expression of connective tissue growth factor can potentially counteract stricture formation. Animal studies allow the assessment of grafts at serial time points, which is not possible in the clinical setting. Hence, development of non-invasive novel imaging modalities that would permit *in vivo* assessment

of TE grafts would be helpful. Regeneration of corpus spongiosum (CS), which is fibrosed in urethral stricture disease[37] and partially absent in hypospadias,[38] needs further investigation. Current TE grafts are geared towards regenerating the epithelium and not the CS. The CS provides mechanical support and blood supply to the urethra[39] and thus it is hypothesised that, due to the absence of CS, urethral reconstructions may fail in the long term.[40] Therefore, engineered spongiosum tissue together with urethral mucosa may provide a better blood supply and mechanical protection of the urethra and better functional outcome. Another technique that should be investigated is the use of three-dimensional (3D) printing. 3D printing can process multiple cell types and multiple biomaterials simultaneously and so could fabricate complex tissues. 3D printing overcomes the limitations with traditional TE methods; namely, poor control of scaffold microarchitecture, difficulties in homogenous seeding of the scaffold, and inability to spatially distribute multiple cell types.[41] 3D printing also has the ability to create customised TE grafts for each patient. Investigation into 3D printing for this purpose is underway.[42]

Further research should be aimed at making these TE strategies truly off-the-shelf. This can be achieved with the use of allogeneic cells that can be either seeded on scaffolds and cryopreserved or delivered to the defect site at the time of surgery by mixing them with novel biomaterials to form *in situ* paste or hydrogels. Further research should also be aimed at developing minimally invasive techniques for TE urethroplasty. One such technique could be excision of strictures endoscopically with the use of a laser and applying the off-the-shelf allogeneic cell paste to the excised area for tissue regeneration.

Continuous collaboration among various disciplines, such as developmental biology, cell biology, biomaterial science, and surgery, are needed to further advance urethral TE.

CONCLUSIONS

Cell-based TE urethral substitutes have encouraging clinical results; however, more clinical experience is warranted.

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Aetiology and Evaluation of Men with Urethral Stricture and the Current Role of Urethroplasty in the Treatment of Anterior Urethral Strictures

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Abstract

The estimated prevalence of urethral stricture disease is 229–627 per 100,000 males, though there are regional variations. Trauma, either from external force or iatrogenic causes, is currently the most common single cause of urethral stricture, although, as with prevalence, there are geographical variations. The presentation usually occurs with lower urinary tract symptoms, sometimes with urinary retention and, rarely, with watering can perineum. The symptoms are best evaluated with a combination of the American Urological Association (AUA) Symptom Index and urinary flow rate measurements for both new cases and suspected recurrences.

Time-tested retrograde urethrography remains the gold standard for a confirmatory diagnosis; however, it is limited by its inability to evaluate the posterior urethra and associated morbidities, such as abscesses and fistulas, thus three-dimensional imaging techniques are emerging as adjunct investigations. These modalities are not currently used universally, but their unavailability is not expected to be a serious hindrance to decision-making by a versatile reconstructive urologist.

Urethroplasty is regarded as the gold standard treatment for urethral stricture; excision and primary anastomosis, buccal mucosa graft, skin graft, and pedicle flap techniques have all been used. Notably, buccal mucosal graft urethroplasty has gained popularity above the others because of its versatility and success rate; this is considered to equate to urethral tissue engineering, which is at present confined to only a few centres.

INTRODUCTION

Urethral stricture disease is common and constitutes a large proportion of the urologist's workload. The prevalence is estimated to be 229–627 per 100,000 males[1] and its effects on the quality of life of those with the disease are far-reaching. In the UK, according to NHS statistics,[2] since the start of the 21st century, 12,000 men have required an operation for urethral stricture, at an annual cost of £10 million and with an increasing prevalence in young men to 1 in 1,000 in men >65 years. Ekeke and Amusan[3] documented a male-to-female ratio of

31.3:1.0 in Port-Harcourt, Nigeria, indicating that urethral stricture is very rare in females.

Gonococcal urethritis has been surpassed by strictures from trauma, lichen sclerosus (LS), transurethral resection of the prostate, open prostatectomy, post hypospadias repair, instrumentation, radiotherapy, and catheterisation.[4,5] There are, however, temporal and geographical variations in the prevalence of the disease and the contribution of the different aetiologies.[6] This, to a large extent, depends on the level of development and available healthcare resources.[7] In the developing world, there are differences and variations in the reported contribution of the different aetiologies;[7,8] however, there is uniformity in reporting trauma as the predominant aetiology in the developed world.[9,10] Many authors have documented the bulbar urethra as being most commonly involved.[8,9]

The treatment of urethral stricture often depends on the expertise available; patients' treatment choices have continued to evolve over the years.[6] Dilatation was the first treatment used, but it has become disfavoured with many urologists now preferring urethroplasty, irrespective of the site and aetiology.[11] In a nationwide survey in the Netherlands, direct vision internal urethrotomy was practiced by 97% of urologists, whereas urethroplasty was performed by only 6–23%.[12] Urethrotomy is also falling out of favour as urethroplasty techniques continue to be refined. The aim of this review is to assess the current aetiology and evaluation of men with urethral stricture and the role of urethroplasty in the management of anterior urethral strictures.

AETIOLOGY OF URETHRAL STRICTURE

Historically, gonococcal urethritis was most commonly responsible for stricture formation in the urethra. Early studies[1,4,9] indicated that urethritis was the most common cause, accounting for up to 50% in some series. Urethral stricture patients also presented late with complications such as urinary retention and watering can perineum; this posed serious challenges to treatment.[13] Urethritis has now been surpassed in most parts of the world by trauma.

In the USA, >2.8 million people are hospitalised annually because of trauma, costing approximately $406 billion per year in medical expenses and productivity loss.[14] Pelvic fracture results from high energy impact and is often indicated by the presence of urethral or bladder injury, or both. Pelvic fracture urethral distraction injury occurs in 4–19% of male pelvic fractures and 0–6% of female pelvic fractures and has been documented to have a prevalence of 5–25%;[4] however, the National Trauma Data Bank® (NTDB) recently placed this figure at 1.4%.[15] This narrowing of the posterior urethra is referred to as stenosis. Urethral injury with subsequent narrowing may also result from a fall astride or penetrating injury from a stab or gun shot.

Many authors have reported iatrogeny as the most common cause of urethral stricture, particularly in the developed world where healthcare intervention is more prevalent. Such interventions include hypospadias repair, cystoscopy, transurethral resection of the prostate, open prostatectomy, radiotherapy, and urethral catheterisation. Lumen et al.[5] documented iatrogenic trauma from the above as the most common cause of urethral stricture, whereas only 19.07% in the study by Ekeke and Amusan[3] were iatrogenic in origin. Urethral stricture has been documented to occur in 2% of men following external beam radiotherapy and 12% after brachytherapy.[16] Malignancy of the urethra may actually masquerade as urethral stricture.

LS is considered an autoimmune inflammatory disease with a predilection for the anogenital region.[17,18] According to Barbagli et al.,[19] the true incidence of urethral involvement in patients with genital LS is unknown. However, approximately 8–16% of men affected by LS are said to develop urethral stricture and, while it is the most common cause of panurethral stricture,[4,18] it accounts for 13.5% of the aetiology of urethral stricture.[20] In some men, a cause for stricture cannot be found and these cases are therefore referred to as either congenital or idiopathic. According to Mundy,[21] many idiopathic strictures are so called because their cause has been forgotten over the years; they are extremely common in the developed world.[22]

DIAGNOSIS OF URETHRAL STRICTURE

History and Physical Examination

Historically, male urethral stricture patients present with progressively increasing lower urinary tract symptoms with or without an obvious cause. According to Alwaal et al.,[4] patients experience weak stream, straining to urinate, incomplete emptying, post-void dribbling, urinary retention, and recurrent urinary tract infection. Complications such as Fournier's gangrene, obstructed ejaculation, urethrocutaneous fistulas, and acute or recurrent prostatitis and epididymoorchitis may be obvious at presentation. A weak stream, frequency, and incomplete voiding were, according to Nuss et al.,[23] noted to be the most prevalent symptoms in patients undergoing urethroplasty for anterior urethral stricture. As the bladder decompensates, it becomes palpable, and acute or chronic urinary retention may occur. Overall, the symptoms are those of bladder outlet obstruction and, in cases that present late, perineal fistulas may be seen. A combination of urinary flow rate and the American Urological Association (AUA) Symptom Index is useful in early diagnosis of new cases and suspected recurrences.[24]

Imaging for Urethral Stricture

The confirmatory diagnostic procedure of choice for urethral stricture should be able to locate the stricture, determine the site, and assess the depth of spongiofibrosis.[25] Currently available procedures do not individually combine these qualities; therefore, diagnosis requires direct visualisation, sonography, and contrast imaging. Retrograde urethrography (RUG) (Figure 1) is the gold standard in the investigation of urethral stricture disease.[26] In the static type (Figure 1B and 1C), the film is taken following injection of the contrast. The posterior urethra is not visualised, as the contrast is milked into the bladder before the film is obtained. Therefore, this type cannot be completely relied on in posterior urethral disease as it visualises only the anterior urethra.[27] The dynamic type (Figure 1A) is done under fluoroscopy for the immediate diagnosis of urethral disease.

Dynamic RUG has the advantage of being able to visualise the posterior urethra and has a sensitivity and specificity of 90%.[28] However, limitations include the requirement for clinical expertise, exposure to sepsis, anaphylactic reaction to contrast media, and associated radiation risk.

Voiding cystourethrography (VCUG) provides information on the dynamics of voiding and occult processes proximal to the stricture, but has the tendency to underestimate length in the bulbar urethra.[20] Both VCUG and RUG can completely overlook complicating features such as fistulas, diverticula, and abscesses, because of which three-dimensional (3D) imaging modalities are emerging in the evaluation of urethral stricture disease.

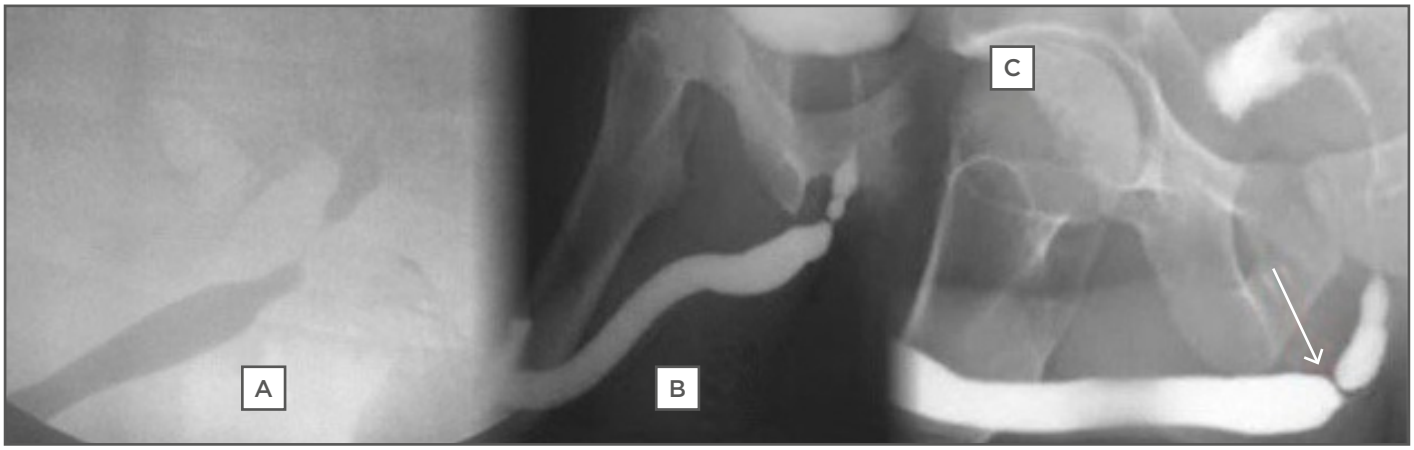

Figure 1: Retrograde urethrography images: A) dynamic; B) static; C) static showing bulbar stricture.

Three-Dimensional Imaging

Ultrasonography (US) is an adjunct to RUG in defining the degree of spongiofibrosis and has better precision in diagnosing anterior urethral stricture. US has the capacity to delineate complications, such as abscesses and diverticula, and it is presently considered to be more precise in determining stricture length and location.[21] US has comparable accuracy to RUG and magnetic resonance urethrography (MRU); it is, however, more successful than RUG in the characterisation of urethral lumen. Similar to the static RUG, US is unable to assess the posterior urethra.[29]

Magnetic resonance imaging (MRI) was first used in 1992 in an attempt to overcome the above limitations of RUG, VCUG, and US.[30] It has been found to be able to determine the degree of urethral distraction, direction of prostate displacement, and defect length.[31] Findings on MRU correlate more with intraoperative findings than RUG and VCUG, and it provides better information on spongiofibrosis.[32] MRU limitations include cost, claustrophobia, need for expertise, limited availability, and incompatibility with implants.

Three-dimensional computerised tomographic urethrography is able to evaluate the location and length of distraction defect, the relationship of the pelvic bone to the urethra, and associated pathology in posterior urethral stricture.[33] There are presently no indications that 3D imaging techniques, particularly MRI, are commonly used in the evaluation of men with urethral stricture.

The Role of Urethroplasty in the Treatment of Anterior Urethral Stricture

Urethral stricture disease remains the most common indication for urethroplasty. Over the decades, several urethroplasty techniques have emerged and continue to be refined as the pathology and dynamics of urethra stricture become clearer. Its use as a gold standard treatment of this disease[22] is presently hampered by the limited number of trained reconstructive urologists and, according to Heyns et al.,[34] limited theatre space, the presence of comorbidities, increased age, and, in some climes, speed of surgery and rural geography.[35] According to the National Practice Survey Board of Certified Urologists in the United States,[36] approximately half of American urologists do not perform urethroplasty, implying that this modality is not fully utilised. Data from the NHS in the UK during 2006 showed that direct vision internal urethrotomy or urethral dilatation was used in 93% of cases and urethroplasty in only 7%.[37]

Controversies also exist regarding the use of flaps and grafts, one-stage and staged procedures, and dorsal or ventral onlay, particularly in LS-induced and post hypospadias repair urethral strictures.[38] On the whole, a good urethroplasty technique should be easily reproducible and result in a straight, good calibre urine stream. Direct vision internal urethrotomy is the most commonly performed procedure for urethral stricture despite its poor success rate. The current recommendation considered the most cost-effective is to refer patients for urethroplasty after a single failed urethrotomy.[10]

Bulbar Urethra

The bulbar urethra is the segment most amenable to different urethroplasty techniques. It is easily accessed (Figure 2A) for excision and primary anastomosis (EPA), one-stage substitution, and staged substitution urethroplasty with flaps or graft using buccal mucosa or skin.[38]

Excision and Primary Anastomosis

Following exposure, as in Figure 2A, the urethra is dissected circumferentially, the extent depending on the length of the stricture, often extending to the bulb proximally and the penobulbar junction distally. Scar tissue is completely excised and the two ends of the urethra are spatulated and anastomosed around an indwelling catheter. Excessive excision of the urethra causes buckling of the penis and this may cause painful penile erection and uncomfortable sexual intercourse.[39] The bulbar urethra can accommodate excision of 2 cm length, which is currently regarded as the comfort zone beyond which chordee may occur, though there are authors who advocate that up to 5 cm of this segment can be excised safely.[40]

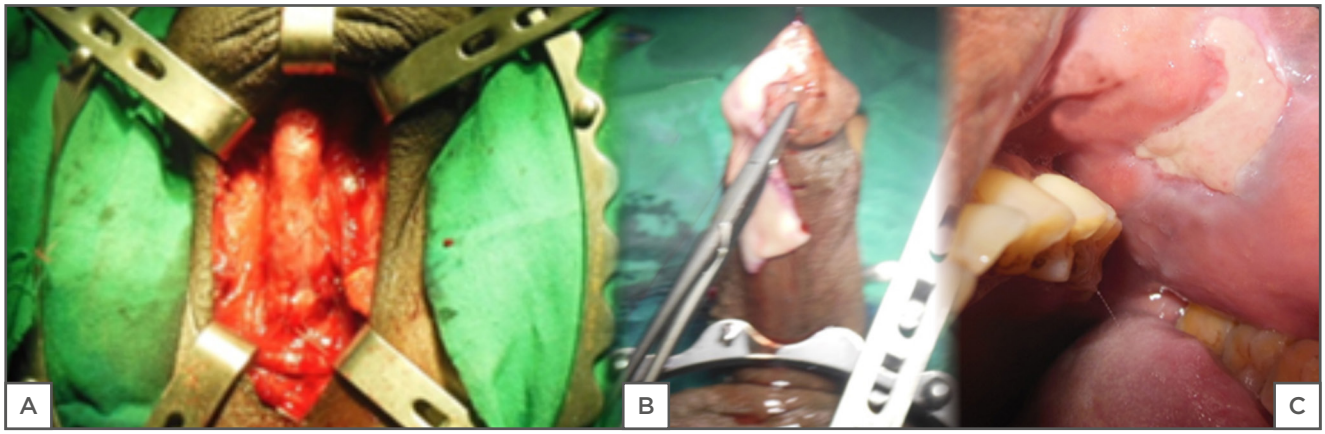

Figure 2: A) Exposed urethra; B) buccal mucosa; C) donor site.

Siegel and Murey[41] expressed the opinion that EPA is the treatment of choice in men with bulbar urethral stricture following a 25-year meta-analysis of contemporary EPA. With a success rate of 90%, it was concluded that it is superior to other methods of treatment. Currently, urologists are concerned about transecting the urethra,[42] particularly in post hypospadias repair, and as such EPA is falling out of favour. Zimmerman and Santucci[11] referred to the ascendance of BMG urethroplasty above EPA as the preferred procedure for bulbar urethral stricture. However, it still has a strong indication in traumatic strictures, as the urethra is considered to have been transected at the time of the injury, especially in men with reasonable comorbidities.

Buccal Mucosa Graft Urethroplasty

BMG was introduced by Humby in 1941.[43] It has favourable characteristics, such as early growth and graft survival, hairlessness, and compatibility with wetness, and has therefore emerged as a great reconstructive material for urologists (Figure 2B). Following exposure of the urethra (Figure 2A), a dorsal, ventral, or lateral stricturotomy approach may be used to patch the urethra.[6] Kulkarni and Barbagli[44] advocate placement of the graft ventrally in the proximal bulbar urethra and dorsally in the distal segment, depending on the clinical situation; this is also the author's current practice. Ventral onlay requires less urethral dissection and has been documented as providing excellent results irrespective of the site and aetiology of the stricture.[45] In BMG urethroplasty, the donor site may be closed or left open (Figure 2C); the latter has the advantage of causing less pain and numbness.

The BMG technique is particularly suited for men with LS-induced urethral stricture, in whom the use of skin is contraindicated, and in post hypospadias repair, in whom urethral transaction is of immense concern.[46] The use of flaps in bulbar urethroplasty has waned as a result of the remarkable success achieved with BMG, which has been documented at >90%.[47] Many renowned reconstructive urologists currently prefer bulbar stricturotomy and a BMG patch;[6,48] however, flaps are still useful in redo cases when scarring is marked and the blood supply is less than adequate.[49]

Staged Urethroplasty

A staged approach to the reconstruction of the bulbar urethra is still sometimes adopted. Indication for this includes a hypoplastic urethral plate, the presence of infection, multiple fistulation either from the infection or trauma of urethral dilatation, previous failed repair, and the presence of comorbidities; in these cases, the urethra cannot be graft enlarged.[50] The urethra can be exposed (Figure 2A) using a median raphe or a U-shaped incision followed by a ventral stricturotomy, which allows for inspection of the urethral plate. If the plate is judged to be unhealthy, it is marsupialised to the skin and retubularisation is completed in 3–6 months. In LS where the use of skin is

contraindicated, the hypoplastic urethra is completely excised and replaced with BMG or patched dorsally during the first stage. It has been documented that perineal urethrotomy is well accepted in communities accustomed to seated or squatted voiding.[51]

PENDULOUS URETHRA

BMG, skin graft, flaps, one-stage and staged urethroplasty are all applicable in penile urethra reconstruction, unlike EPA, which is contraindicated because resection of even a short segment of the penile urethra causes chordee of the penis.[52] Barbagli et al.[53] recently described their approach to reconstruction of the penile urethra in men with stricture of this segment. They advised that in patients with LS, the use of buccal mucosa at the first stage is mandatory because LS does not affect the oral mucosa, while those with a history of failed hypospadias repair presenting with obliterative strictures, associated fistulas, scarred penile skin, chordee, abnormal meatus, small glans, and deficiency of the dartos layer may require a two-stage repair, using the buccal mucosa in the second stage. According to them, the majority of patients presenting with penile strictures not related to LS or failed hypospadias repair are good candidates for one-stage urethroplasty using a graft or flap.

In the one-stage technique, the urethra is opened ventrally, patched dorsally with a BMG, and closed ventrally (Asopa).[54] In the staged procedure, the dorsal BMG patch is done during the first stage, but the urethra is sutured to the adjacent skin margin and retubularisation is done in the second stage. However, in the Johansson staged urethroplasty, the dorsal BMG patch is omitted while the urethra is marsupialised to the skin (Figure 3A). The urethra is expanded by taking adjacent skin with it during retubularisation at the second stage. This approach has its advocates, disadvantages, advantages, indications, and contraindications.[52,55,56]

Orandi[55] and Quartey[56] described the reconstruction of the anterior urethra using a pedicled skin flap. The principles of these single-stage procedures still remain valid in the treatment of non-obliterative penile urethral strictures that are not LS-induced. The multiplicity of these techniques requires the approach to each patient to be individualised, taking into consideration the patient's desire, aetiology of the stricture, previous failed repairs, and the sexual functioning of the penis.

PANURETHRAL STRICTURE

Panurethral stricture poses a great challenge to the reconstructive urologist, because of the high level of surgical experience and expertise it requires, and also to the patient, as repair has a significant potential for morbidity. Two distinct approaches are described here.

Kulkarni's Panurethroplasty

Kulkarni et al.[57] described a one-stage reconstruction of the entire urethra in men with panurethral stricture. This involves exposing the urethra via a perineal incision (Figure 2). Through the incision, a one-sided dissection and penile invagination allows the entire anterior urethra to be exposed. This is followed by a dorsal stricturotomy and a BMG patch (Figure 3B). It requires harvesting of buccal mucosa bilaterally and it is therefore an extensive surgery.

Kulkarni et al.[57] documented a success rate of 84.9% with this procedure and described the advantages as including the perineal approach, which avoids a penile incision and suture line, minimisation of the risk of urethrocutaneous fistula, excellent cosmesis, reduced incidence of chordee, and preservation of the bulbospongiosus muscle.

Staged Approach

Panurethral reconstruction can also be approached in two stages by repairing the bulbar segment using a ventral or dorsal on-lay BMG urethroplasty and first-stage Johansson (Figure 3A) for the penile urethra at the same setting. The penile urethra is tubularised by augmenting it with adjacent penile skin or dorsal BMG in the second stage. This was described by Zimmerman and Santucci[11] in 2011, but appears to have been overshadowed by the panurethroplasty of Kulkarni, because staged procedures are said to be fraught with technical issues such as multiple revisions.[58]

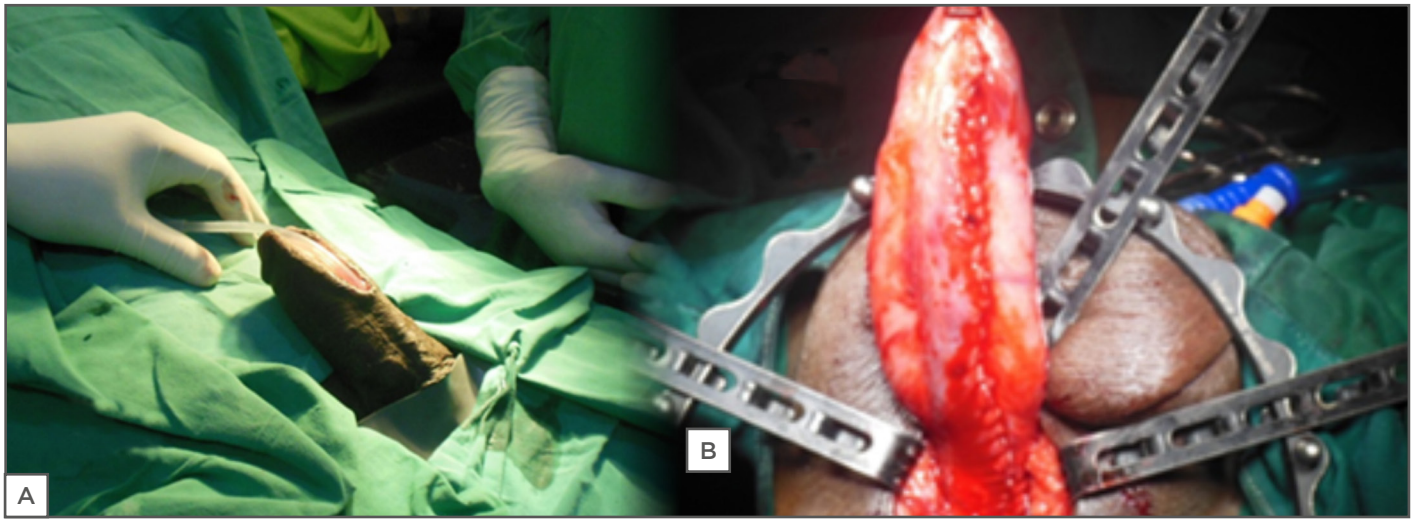

Figure 3: A) Second-stage Johansson's urethroplasty; B) Kulkarni's panurethroplasty.

Technical expertise, complexity of the stricture, the state of the urethral plate, presence of comorbidities and infection will sometimes favour the use of a staged approach. A single-stage panurethroplasty is an enormous undertaking and therefore requires effective patient selection, as a perineal urethrotomy may even be acceptable and adequate for some men with reasonable comorbidities. The authors have seen men with a stone lodged in their urethra proximal to the stricture with severe infection and poorly controlled diabetes.

Tissue Engineering

Substitution urethroplasty using skin or buccal mucosa is the standard treatment for urethral stricture disease. Substitution surgery is associated with increased morbidity and limited availability of substitute material. This led to the development of interest in urethral tissue engineering. Results of tissue engineered repairs are currently considered to be similar to standard repairs, though its use at present is limited to failed previous repairs in a few centres.[59]

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Does the Use of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Improve Survival in Bladder Cancer?

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Abstract

Introduction: The use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) has been associated with improved bladder cancer outcomes. The objective of this study was to perform a systematic review of the literature and investigate the effects of these medications on survival from our own retrospective database.

Methods: A systematic literature search of PubMed and the Cochrane database was conducted and 34 relevant articles identified. No randomised control trials were identified. After exclusion, five observational studies were included in our analysis. Since there was a paucity of data, we then performed a retrospective cohort study using clinical data from our electronic medical record. All patients who underwent radical cystectomy, with or without adjuvant chemotherapy, at a single tertiary care centre in Ontario, Canada between 2001 and 2016 were identified.

Results: Our literature review found that ACEI or ARB use in upper urinary tract and lower urinary tract non-muscle invasive bladder cancer was associated with increased 5-year recurrence-free, cancer-specific, and overall survival. Our own analysis identified 464 patients who underwent radical cystectomy for muscle-invasive bladder cancer during the study period. Ninety-nine individuals received ACEI or ARB treatment during this time. Cox-proportion hazards modelling suggested that the use of ACEI or ARB was not significantly associated with a survival benefit.

Conclusions: We are unable to support or oppose the use of ACEI or ARB as adjuvant treatment in bladder cancer due to the heterogeneity and quality of published data. Our own study data do not support the use of these medications as adjuvant therapy for muscle-invasive bladder cancer. A randomised control trial in this area of research is required.

INTRODUCTION

Bladder cancer is the ninth most common cause of cancer worldwide and was associated with 165,000 deaths in 2012.[1] The incidence of bladder cancer is much higher than its associated mortality rates, but it is among the most expensive cancers to treat and monitor, with a significant proportion of the costs attributable to high rates of recurrence and progression.[2] Although high-quality evidence supports intravesical Bacillus Calmette–Guérin (BCG) therapy and neoadjuvant chemotherapy to prevent disease recurrence in non-muscle invasive bladder cancer (NMIBC)[3] and muscle-invasive bladder cancer (MIBC),[4] recurrence rates remain high. There has been considerable interest in the identification of adjuvant treatments to improve disease outcomes.

Angiogenesis, induced by angiotensin II (AngII) and other factors, is necessary for tumour growth.[5] Angiotensin II Type 1 receptor (AT1R) is associated with various malignancies, including melanoma, pancreatic cancer, breast cancer, and bladder cancer.[6,7] Its role in angiogenesis, growth, and metastasis of tumour cells is well-established.[8,9] Activation of this receptor via the AngII–AT1R signalling pathway leads to vascular endothelial growth factor (VEGF) expression, stimulating tumour angiogenesis. Furthermore, the AngII–AT1R signalling pathway promotes macrophage mobilisation and infiltration into the tumour bed, mainly secondary to monocyte chemoattractant protein-1.[7] This chemokine acts as a prominent regulator of tumour growth, aggression, and migration, and ultimately promotes tumour cell survival.[8] The AngII–AT1R signalling pathway has been shown to cause increased expression of VEGF. Since the AngII–AT1R signalling pathway upregulates VEGF, the suppression of Ras may impede or even prevent angiogenesis, which is necessary for sustained tumour growth.[6,7,10] Therefore, it is speculated that the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) may influence the outcome of malignant tumours, including bladder cancer.[8,11] The objective of this study was to perform a systematic review of the literature and investigate the effects of ACEI and ARB use on survival from our own retrospective database.

METHODS

Phase 1

A systematic review of the literature was performed according to the methods developed by the GRADE Working Group.[12-14] A focussed clinical question was formulated that directed comprehensive literature searches for high-quality research articles. All study types were considered due to the paucity of data. Disease-specific and overall survival (OS) were considered critical outcomes of interest; disease recurrence was considered a secondary outcome of interest.

A systematic literature search was conducted on PubMed (1966–2017) using the MeSH search terms: "Urinary Bladder Neoplasms"[MeSH] AND "Angiotensin Receptor Antagonists"[MeSH]. The search was limited to clinical trials with a human population in the English language. The Cochrane database was also searched for relevant high-quality systematic reviews on this topic. A snowballing technique was used from identified articles and recent published systematic reviews within this area to ensure a comprehensive search to identify additional articles for inclusion within our systematic review.

Study information was abstracted by a single reviewer and entered into RevMan. The quality of evidence informing each clinical question was rated on an outcome-specific basis as high, moderate, low, or very low according to GRADE.[12] Dimensions of evidence quality considered were risk of study bias, inconsistency, indirectness, imprecision, and publication bias. These steps were performed independently by two reviewers; disagreements were resolved by discussion. Abstracted data were subsequently transferred into GRADEPRO and used to generate evidence profiles in the standard GRADE format.

Phase 2

It was established that there was a lack of high-quality data regarding outcomes associated with ACEI and ARB use in bladder cancer; thus, this review was augmented with an analysis from the authors' own dataset.

Study Design and Setting

A retrospective cohort study was conducted using clinical data from an electronic medical record. All residents of Ontario (population: 13 million) have access to a government-administered single-payer healthcare system.

Population

All patients who underwent radical cystectomy, with or without adjuvant chemotherapy, were identified at a single tertiary care centre in Ontario, Canada, between 1st August 2001 and 30th June 2016. There were no exclusion criteria.

Outcomes and Exposures

The primary outcome was survival, defined using death as documented in the authors' electronic medical records from the time of cystectomy. The main exposure of interest was use of ACEI or ARB identified by chart review. There were several other exposures also included.

Demographic characteristics

Sex, age, American Society of Anesthesiologists (ASA) score, medical comorbidities (cardiovascular, metabolic, musculoskeletal, gastrointestinal, pulmonary, genitourinary, neurological, and oncological), previous surgery, previous pelvic radiation, presence of radiation cystitis, lifetime smoker status, current smoker status, medication history (metformin, pioglitazone, rosiglitazone, statin, renin-angiotensin inhibitor), and vegetarian status.

Perioperative characteristics

Number of transurethral resections of bladder tumours (TURBT), number of bladder lesions on cystoscopy, localisation of bladder lesions, histological diagnosis from TURBT, date of referral from primary caregiver, symptoms at initial consultation with a urologist, date of cystectomy, perioperative blood loss, hospital stay length, operative time, urinary diversion type, neoadjuvant treatment status, and adjuvant treatment status.

Postoperative characteristics

Cystectomy histopathology, tumour grade, pathologic T-stage, presence of non-invasive flat carcinoma, number of positive nodes, presence of prostate cancer, pathologic T-stage of prostate cancer, presence of prostatic intraepithelial prostate cancer, presence of atypical small acinar proliferation within the prostate, proportion of the prostate involved by primary tumour, Gleason score, presence of positive margins, number of lymph nodes, presence and grade of tumour in ureter on frozen section, and tumour extension into the vagina and/or urethra.

Follow-up characteristics

Postoperative pelvic radiation, recurrence of cancer, date of recurrence, pain at recurrence, site of recurrence (lymph node, pelvis, bowel, liver, lung, and bone), death, cause of death, and date of last follow-up.

Statistical Analyses

Baseline variables are reported as medians (interquartile range [IQR]) or counts (percentages) and were compared using student's T-test for continuous variables, and Chi-square test for categorical variables. A two-sided $p<0.05$ was considered significant. Differences in survival rates were assessed using Kaplan–Meier survival estimates with Cox-proportion hazards modelling.

RESULTS

Phase 1

The clinical question constructed was: 'Do angiotensin converting enzyme inhibitors or angiotensin II receptor blockers affect bladder cancer outcomes?'

Literature Search

A total of 41 articles were identified for review. Of these 41 articles, after reviewing the title and abstracts, 35 articles were removed for non-relevance. The remaining 6 articles were comprehensively reviewed, and 1 was excluded for for non-relevance, leaving 5 articles for inclusion in this study.

Evidence

No randomised control trials were identified. A total of five observational studies were included in the analysis; these studies examined the effect

of ACEI or ARB use on outcomes related to several components of the urinary system.

Two studies examined outcomes associated to lower urinary tract NMIBC post-TURBT. Blute et al.[6] performed a retrospective cohort study of 340 patients with NMIBC post-TURBT, identified using an institutional bladder cancer database. It was found that ACEI or ARB use was associated with reduced tumour recurrence (relapse-free survival [RFS]) (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.45–0.84; p=0.005) but not improved progression-free survival (HR: 0.6; 95% CI: 0.19–1.97; p=0.400) on multivariate analysis. A Kaplan–Meier analysis showed that 5-year RFS was 45.6% in individuals who received ACEI or ARB compared to 28.1% in those who did not (p=0.01). Yuge et al.[9] performed a retrospective cohort study of 330 patients with NMIBC post-TURBT, identified on chart review. They found that lack of ACEI or ARB use was associated with worse RFS (HR: 2.26; 95% CI: 1.22–4.19; p=0.010) but not associated with risk of stage progression on multivariate analysis. Kaplan–Meier analysis showed that 5-year RFS rate was 78.4% in individuals who received ACEI or ARB compared to 53.3% in those who did not (p=0.017).

One identified study analysed outcomes associated with lower urinary tract MIBC radical cystectomy. Yoshida et al.[15] performed a retrospective cohort study of 216 patients post-radical cystectomy from chart review at three institutions. The study found that ACEI or ARB use was associated with improved cancer-specific (CSS) (HR: 0.47; 95% CI: 0.23–0.95; p=0.036) and OS (HR: 0.36; 95% CI: 0.18–0.73; p=0.02) on multivariate analysis. Kaplan–Meier analysis showed that the 10-year OS rate was 71.3% in individuals who received ACEI or ARB compared to 47.7% in those who did not (p=0.0097).

Table 1: GRADE evidence profile for the question: Do angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers affect bladder cancer outcomes?

Certainty assessment							Summary of findings				
Number of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Control	Intervention		Risk with control	Risk difference intervention
Overall survival											
860 (3 observational studies)	Very serious*	Very serious†	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	⊕OOO Very low	228/667 (34.2%)	47/193 (24.4%)	Not estimable	342 per 1,000	342 fewer per 1,000
Disease recurrence											
982 (3 observational studies)	Serious*	Very serious†	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	⊕OOO Very low	364/699 (52.1%)	103/283 (36.4%)	Not estimable	521 per 1,000	521 fewer per 1,000
Disease progression/metastases free survival											
279 (1 observational study)	Serious*	Serious†	Serious‡	Serious§	All plausible residual confounding would suggest spurious effect, while no effect was observed	⊕OOO Very low	57/231 (24.7%)	4/48 (8.3%)	Not estimable	247 per 1,000	247 fewer per 1,000

*Retrospective cohort study; †different disease sites; ‡different interventions between groups; §small overall number of participants.

CI: confidence interval.

Two studies were identified examining outcomes associated with upper tract urothelial carcinoma post-nephroureterectomy (nephroU).[16,17] Yoshida et al.[16] performed a retrospective cohort study of 312 patients post-nephroU identified on chart review at four institutions. They found that ACEI or ARB use was associated with improved RFS (HR: 0.48; 95% CI: 0.27–0.87; p=0.015), CSS (HR: 0.31; 95% CI: 0.15–0.65; p=0.002), and OS (HR: 0.45; 95% CI: 0.26–0.78; p=0.004) on multivariate analysis. Kaplan–Meier analysis demonstrated 5-year OS was 68.7% in individuals who received ACEI or ARB compared to 61.8% in those who did not (p=0.047). Tanaka et al.[17] performed a retrospective cohort study of 279 patients post-nephroU on chart review at two institutions. It was found that a lack of ACEI or ARB use was associated with worsened metastases-free survival (HR: 3.14; 95% CI: 1.14–8.67; p=0.027) but not associated with CSS on multivariate analysis. Kaplan–Meier analysis showed that 5-year OS was 85.8% in individuals who received ACEI or ARB compared to 73.7% in those who did not (p=0.047).

These studies were then evaluated for quality using GRADE criteria. The critical outcomes for this question were defined as related to OS, disease recurrence, and disease progression or metastasis-free survival. No data on complications were presented in any of the studies (Table 1).

Clinical Implications

Unfortunately, a recommendation cannot be made that either supports or opposes the use of ACEI or ARB as adjuvant therapy for bladder cancer, because of the low quality and heterogeneity of the published data. The results presented within this literature review are encouraging that these medications could offer a significant survival benefit with a minimal and well-established toxicity profile. Randomised control trial data are needed within this area of research.

Phase 2

A total of 464 patients were identified who underwent radical cystectomy during the study period, of whom 354 (77.5%) were male and were of median age of 71 years (IQR: 63–76) and median ASA score of 3 (IQR: 3–3). Patients had a variety of comorbidities, including cardiovascular disease (66.70%; most commonly hypertension, which appeared in 152 [44.00%] patients), metabolic disease (65.00%; most commonly hypercholesterolaemia, which appeared in 72 [21.50%] patients), genitourinary disease (13.20%; most commonly benign prostatic hyperplasia, which appeared in 34 [12.45%] patients), and pulmonary disease (12.90%; most commonly chronic obstructive pulmonary disease, which appeared in 28 [10.00%] patients). Approximately half (n=182 [42.30%]) of patients had previously smoked and 21.85% (n=94) continued to smoke at the time of surgery. Patients commonly presented with haematuria (n=115 [44.7%]) or multiple symptoms, including frequency, urgency, or urinary retention (n=127 [49.4%]). Preoperatively, 22.6% of patients (n=99) received neo-adjuvant chemotherapy. Statistical analysis revealed no difference between the total cohort, patients with disease recurrence, or patients who died during the study period for these characteristics (Table 2).

The majority of patients had undergone a single TURBT (median: 1; IQR: 1–2) with a median of 1 bladder tumour (IQR: 1–3) most commonly located at the trigone (n=19 [11.0%]) and most commonly Stage T2 (n=81 [36.9%]). During radical cystectomy, median blood loss was 500 cc (IQR: 300–800) with a median operative time of 253 minutes (IQR: 226–301). The most commonly performed urinary diversion was an ileal conduit (n=388 [88.5%]). Average hospital stay was 9 days (IQR: 8–12). Statistical analysis revealed an increased risk of having T1 or T2 tumour on TURBT among individuals who died during the study period as compared to the total cohort (Table 2).

Histopathology from RC most commonly showed transitional cell carcinoma (n=375 [86.2%]) of high grade (Grade 3; n=343 [79.7%]) and 122 individuals with positive nodes (28.9%). Thirty-five patients had positive tumour margins (8.2%) and 41.8% were found to have prostate cancer. Postoperatively, 18.1% of patients received chemotherapy. Statistical analysis revealed an increased risk of having a higher stage and grade tumour from RC pathology among individuals with disease recurrence, as compared to the total cohort (Table 2).

Table 2: Cohort baseline characteristics.

	Total cohort (n=464)	Patients with disease recurrence (n=99)	p value	Patients who died (n=127)	p value
Baseline characteristics					
Median age, years (IQR)	71 (63–76)	72.1 (65–76)	0.074	71 (64–78)	0.549
Male sex	354 (77.4%)	233 (78.4%)	0.332	91 (73.3%)	0.089
ASA score	3 (3–3)	3 (3–3)	0.995	3 (3–3)	0.623
Current smoker	94 (21.8%)	65 (22.1%)	0.570	26 (22.0%)	0.601
Operative characteristics					
Median number of TURBT (IQR)	1 (1–2)	1 (1–2)	0.509	1 (1–2)	0.272
Median number of tumours on TURBT (IQR)	1 (1–3)	1 (1–3)	0.275	1 (1–2)	0.700
TURBT pathology:					
Ta	10 (4.5%)	2 (4.8%)	0.994	4 (6.6%)	0.388
Tis	19 (8.6%)	1 (<1%)	0.107	5 (8.3%)	0.988
T1	74 (33.7%)	10 (24.3%)	0.174	13 (21.6%)	0.050
T2	81 (36.9%)	20 (48.7%)	0.062	29 (40.2%)	0.040*
pT3	3 (1.3%)	1 (<1%)	0.564	1 (<1%)	0.942
Blood loss, cc (IQR)	500 (300–800)	500 (300–800)	0.935	500 (300–800)	0.265
Operative time, minutes (IQR)	253 (226–301)	256 (228–310)	0.196	248 (223–298)	0.857
Hospital stay, days (IQR)	9 (8–12)	9 (8–12)	0.723	9 (8–12)	0.441
Ileal conduit diversion	388 (88.5%)	88 (88.8%)	0.114	111 (91.7%)	0.300
Radical cystectomy histopathology					
TCC histology	375 (86.2%)	83 (80.0%)	0.221	103 (86.5%)	0.953
Grade:					
Low grade	30 (6.9%)	6 (6.0%)	0.486	10 (8.4%)	0.156
High grade	343 (79.6%)	86 (86.8%)	0.043	92 (77.9%)	0.382

*Statistically significant.

ASA: American Society of Anesthesiologists; IQR: interquartile range; TCC: transitional cell carcinoma; TURBT: transurethral resection of bladder tumours.

We identified 99 individuals who had received ACEI or ARB during the study period. Kaplan–Meier survival curves were generated comparing survival of individuals who had received ACEI or ARB versus those who had not. Cox-proportion hazards modelling indicated that ACEI or ARB use was not significantly associated with a survival benefit (HR: 1.21; 95% CI: 0.76–1.92; p=0.419) (Figure 1).

DISCUSSION

The literature and the authors' own analyses are unable to support the use of ACEI or ARB to delay recurrence, prevent progression, or improve survival for individuals with bladder cancer. The systematic review of the literature identified that there is a paucity of high-quality literature to guide decision making within this area, because the published studies are of low quality, based on diverse clinical populations, and use a variety of outcomes to assess this clinical question.

There are several important limitations to this study. The authors' own analysis is retrospective in nature, has a relatively short outcome period, and did not collect comprehensive data on the duration, quantity, or type of ACEI or ARB used.

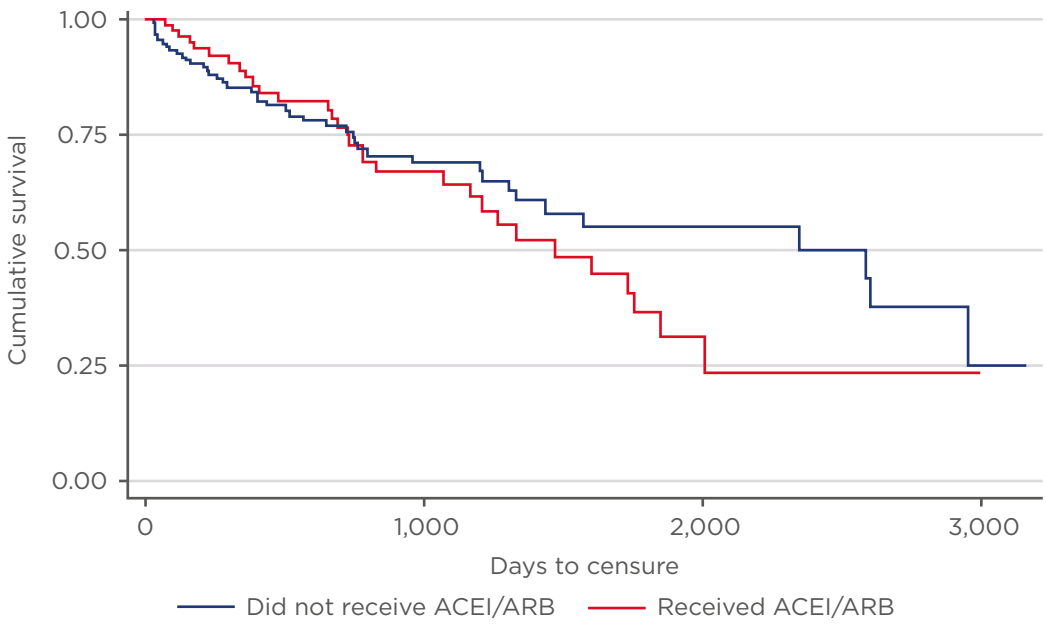

Figure 1: Kaplan–Meier curves from date of surgery to time of death or loss to follow-up by angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker use.

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

The literature review was confined to PubMed and the Cochrane database and was limited to English language papers only. These limitations highlight the need for a high-quality randomised control trial analysing this issue. Given the relatively modest cost associated with ACEI and ARB, this trial would not be overly expensive or require extensive regulatory review. The ideal dose and scheduling of medication would likely reflect current patterns for use in the treatment of hypertension, as per previous observational studies. These medications have well-established side-effect profiles and so should be relatively easy to identify.

Several meta-analyses have been published within this area but are, unfortunately, of very low quality and have provided no clarity for our clinical question. Several meta-analyses have examined whether the use of ACEI or ARB is associated with improved oncologic outcomes across a variety of cancers sites,[18-20] but these studies have grouped the heterogenous articles we have identified and meta-analysed the resulting data; this is an inadequate methodological approach to the data within this area when aiming to guide clinical practice and must be viewed purely as hypothesis-generating. There is a clear need for high-quality randomised control trials within this area, given the encouraging results from observational studies that have been performed to date.

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