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UROLOGY

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Review of
EAU 2017
London, UK

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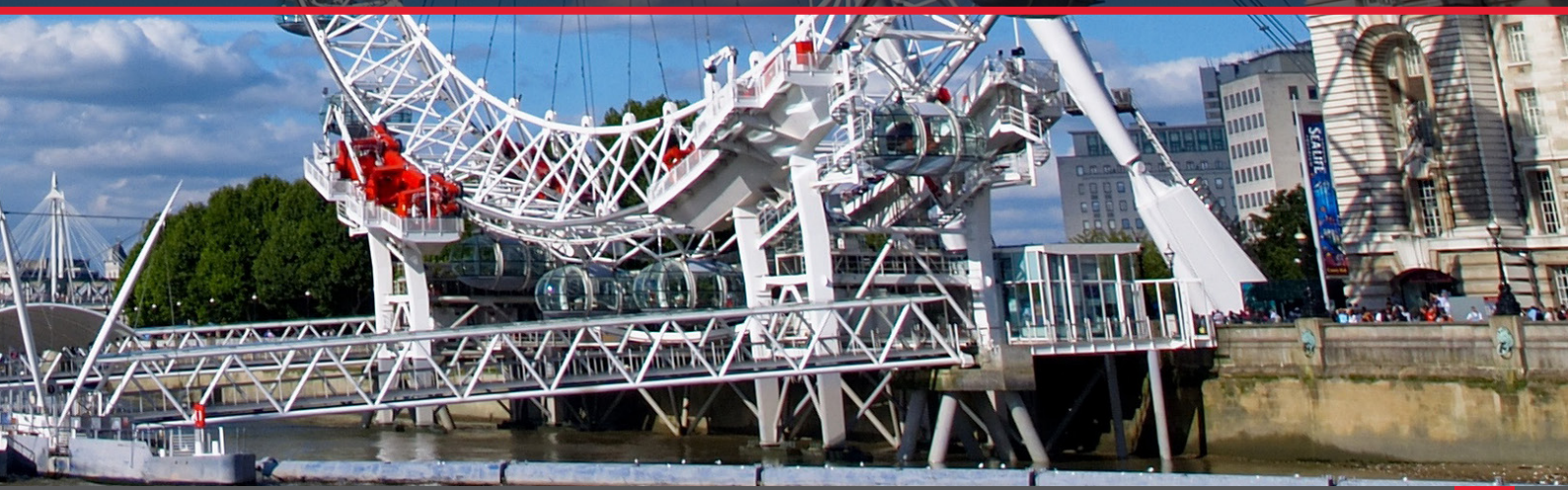
UROLOGY



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Welcome

Greetings and a very warm welcome to the 2017 edition of *EMJ Urology*, where you will find insights into the urological happenings of the last year as well as the European Association of Urology (EAU) 2017 Congress. We are proud to present a dedicated section covering EAU 2017, which features an array of abstract summaries and news highlights from the congress. Dovetailing with this content is our selection of peer-reviewed articles alongside several thought-provoking interviews with members of our Editorial Board, both old and new. In these interviews our Editorial Board members proffer their advice, reflect on the future of the field of urology, and share experience drawn from their careers. This year, we are excited to present an interview with our distinguished Editor-in-Chief Dr Abdullah Erdem Canda.

This year's EAU congress was held in the bustling city of London, UK and saw a range of plenary, expert, and technical sessions highlighting the most recent urological developments. Additionally, >1,100 abstracts were presented, several of which can be found discussed within the pages of this eJournal. We have aimed to capture the essence of the event, which was fertile ground for new ideas to germinate and be shared, in our congress review section.

This year's EAU congress was held in the bustling city of London, UK and saw a range of plenary, expert, and technical sessions highlighting the most recent urological developments.

Our Editor's Pick for this edition is by Ni and Htet and is a thorough consideration of adrenal cortical carcinoma. The authors begin with the pathogenesis of adrenal cortical carcinoma before moving on to cover clinical presentation, diagnosis, and various treatment options such as surgery, radiotherapy, and chemotherapy. Finally, they briefly touch on the prognosis for patients with this condition. Alongside our Editor's Pick are several other stimulating articles: Hermans et al. report on a highly unusual case of an adult male patient incidentally diagnosed with arteriovenous malformation and provide a literature review. Butcher and Serefoglu invite us to consider the topic of premature ejaculation and discuss recent advances in pharmacotherapy of the same. Gómez Rivas et al. have penned a paper that outlines the options available to urologists in cases of determining whether a repeat biopsy should be performed in a patient with a previously negative biopsy result but rising prostate-specific antigen. Finally, Aggarwal et al. have written a clinical review of renal stones and Chokalingam et al. examine the management of anterior urethral structures.

We trust you will find the material contained within *EMJ Urology* both interesting and inspiring and that you obtain valuable knowledge for your practice. If we missed you at this year's EAU congress, we hope to see you at next year's congress in Copenhagen, Denmark!

Spencer Gore

Director, European Medical Journal

Foreword

Dr Abdullah Erdem Canda

Ankara Atatürk Training and Research Hospital, Ankara, Turkey.

Dear Colleagues and Friends,

It is a great pleasure for me to introduce you to the new issue of *EMJ Urology*.

In this issue, we again have a wide variety of very interesting papers including Incidentally detected renal arteriovenous malformation: a case report and review of the literature; Adrenal cortical carcinoma: clinical perspectives; Renal stones: a clinical review; Negative biopsies with rising prostate-specific antigen. What to do?; Recent advances in the pharmacotherapy of premature ejaculation; and Management of anterior urethral strictures.

The European Association of Urology (EAU) Congress is organised every year and attracts great attention worldwide.

The European Association of Urology (EAU) Congress is organised every year and attracts great attention worldwide. Many sessions, debates, presentations, and courses are included in this congress related to every urology subspecialty where the latest developments are presented and discussed. In this issue, you will also have the chance to read brief information about the EAU Congress, which was held from 24th–28th March 2017 in London, UK, and is one of the biggest urology meetings in the world.

I would like to take this opportunity to invite you all to submit your work to *EMJ Urology*.

I hope you enjoy reading the new issue!

Kind regards,

Dr Abdullah Erdem Canda

Professor of Urology, Department of Urology, School of Medicine, Yildirim Beyazit University, Ankara Atatürk Training and Research Hospital, Ankara, Turkey.

EMJ EUROPEAN MEDICAL JOURNAL

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Includes a selection of the latest articles for urology, interventional cardiology, and more.

Featured inside:

FEATURE

Climate Change: What Can Doctors Do?

- Thomas Micklewright

ARTICLES

Editor's Pick: 3D Printing for Biomedical Applications: Where Are We Now?

- Carlos Miguel Chiesa Estomba et al.

Hide and Seek: The Game Between Chronic Lymphocytic Leukaemia Cells and B Cell Receptor Signalling Inhibitors

- Kumudha Balakrishnan et al.

Haemangioma: A Review of the Literature and an Unusual Case Report

- Ajaya Kumar

Transcatheter Repair of Congenital Heart Defects in the Young

- Sonia A. El-Saiedi et al.

Anaesthesia Techniques in Transfemoral Transcatheter Aortic Valve Implantation: A Brief Review

- Mehmet Aksoy et al.

New Drug Treatments for Osteoarthritis: What is on the Horizon?

- Fiona E. Watt, Malvika Gulati

Contemporary Drug-Eluting Stents and Vascular Response

- Anwer Habib et al.

Does Race/Ethnicity Have a Role in a Link Between Lower Urinary Tract Symptoms and Metabolic Syndrome?

- Seong Ho Lee, Sang Kon Lee

Antiphospholipid Syndrome and the Lungs

- Süreyya Yılmaz, Zülfükar Yılmaz

Cardiovascular Risk Factor Control in Type 2 Diabetes Mellitus and New Trial Evidence

- Peter M. Nilsson

State-of-the-Art Advances in Duchenne Muscular Dystrophy

- Henriette Van Ruiten et al.

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EAU ANNUAL CONGRESS 2017

EXCEL LONDON,
LONDON, UK
24TH–28TH MARCH 2017

Welcome to the European Medical Journal review of the 32nd Annual European Association of Urology Congress

The vibrant city of London was the location for this year's Annual European Association of Urology (EAU) Congress, welcoming attendees from across the world with the traditional sounds of a marching band. Taking place over 5 days, the congress included plenary sessions as well as expert and technical sessions reflecting on the most recent developments across the field of urology. In addition, >1,100 abstracts were presented in the form of video presentations or posters during the event. Attendees kept track of everything they wished to participate in with the official EAU Pocket Events App, which also allowed attendees access to the scientific content following the event. In our congress review section,we bring you highlights of the congress to refresh your memory of or to inform those who were unable to attend about all the unmissable urological updates. In his official welcome, EAU Secretary General Prof Christopher Chapple summed up the collaborative nature of the event, stating: "The scale of activities makes our congress a one-stop event where you can connect not only with your colleagues but also create new professional contacts with top-notch researchers and specialists."

In his remarks at the opening ceremony, Sir Bruce Keogh, NHS England's Medical Director and Commissioner of the Commission for Health Improvement spoke of his pride in welcoming the attendees on behalf of the health service, noting: "at these events new ideas begin to take seed and take hold." Sir Keogh cited: "increasing demand, rapidly escalating cost, changing public and professional expectations, and not enough money to serve everything," as the fundamental problems facing healthcare systems around the world, and spoke of his admiration of the work done by EAU and partner associations to foster collaboration between different groups to address these issues and improve healthcare around the world. He also expressed his thanks to colleagues who were designing and developing the tools to allow surgeons and clinicians to bring these changes to their patients.

The opening ceremony also featured the award winners of the congress. This year the most prestigious award, the Willy Gregoir Medal, was bestowed upon

Prof Paul Abrams, Department of Urology, University of Bristol, Bristol, UK, for his significant contributions to the development of the urological specialty in Europe. He commented in the European Urology Today Congress News that: "A challenge for urology is to carry the quality of European urology to the developing countries, and the EAU is doing a great job in starting that process." Also recognised were Prof Per-Anders Abrahamsson, Department of Urology, Skåne University Hospital, Malmö, Sweden, who received the Frans Debruyne Lifetime Achievement Award for longstanding and important contribution to the activities and development of EAU, and Prof Christian Gratzke, Department of Urology, Ludwig-Maximilians-University, Munich, Germany, who was awarded the Crystal Matula for young promising European urologists. Alongside the awards, honorary member titles were given to Prof Shin Egawa (Japan), Prof Tomas Hanus (Czech Republic), Prof Vito Pansadoro (Italy), Prof Eduardo Solsona (Estonia), and Dr Patrick Walsh (USA). A selection of abstracts, papers, and videos were also recognised for their contributions to urology.

The topics covered by the presentations and symposiums were extensive and all-encompassing, with something for every attendee from across the board. In the following review highlights, we present to you the very best of the cutting-edge research and data from across Europe. We hope you will enjoy reading the EAU highlights, and very much look forward to seeing many of you in March 2018, at next year's congress, due to be held in the beautiful city of Copenhagen, Denmark.

> "A challenge for urology is to carry the quality of European urology to the developing countries, and the EAU is doing a great job in starting that process."

Biosensor Chips in the Fight Against Antibiotic Resistance

ANTIBIOTIC overuse and mistreatment is fast becoming a critical public health issue. Part of this can be attributed to the current delay in bacterial isolation and determination of their susceptibility to antibiotics currently available. As described in a EAU press release dated 24th March 2017, a novel technology utilising biosensor chips may be about to change this.

> “If our system can save an extra day in hospital, that alone will save at least $300 in most countries.”

Shockingly, it is estimated that >9,000 patients die from bacterial infections each year in the UK, with 300,000 individuals acquiring such infections within a hospital setting. Across Europe, an annual incidence of >4 million patients developing healthcare-acquired bacterial infections has been reported. The high occurrence of bacterial infections and limitation in the number of effective antibiotics now left available has further augmented the problem of resistance. It is therefore pertinent that a swift, accurate method for diagnosis and treatment recommendation be developed.

Pioneering research led by Prof Ester Segal, Technion Israel Institute of Technology, Haifa, Israel, has trialled the implementation of silicon micropillar arrays in determining the most appropriate antibiotics for the treatment of *Escherichia coli* infection, the leading culprit for urinary tract infections. The silicon biosensor chips designed by the team contain thousands of coated nano wells, equipped to effectively trap the bacteria and allow a count to be calculated and growth measured. Various antibiotic dilutions are then added to each nano well with the aim to inhibit the growth of the colony, a process able to obtain results within just 2–6 hours, compared with the 2-day approach currently used.

Although it is early days, the team are hopeful that their system will be implemented within worldwide clinical practice. Prof Sarel Halachmi, Bnai Zion Medical Centre and Technion Israel Institute of Technology, Haifa, Israel, explained: "If our system can save an extra day in hospital, that alone will save at least $300 in most countries."

New Approach for Prostate Cancer Screening

A NEW technique for prostate cancer (PCa) screening, based on magnetic resonance imaging (MRI), was presented at this year's congress, as noted in a EAU press release dated 25th March 2017. The study's lead author, Dr Arnout Alberts, Erasmus Medical Centre, Rotterdam, Netherlands, spoke excitedly about the potential of MRI-based screening, stating that: "This could change the balance of the equation." Indeed, although PCa is the most common cancer in men worldwide, the current PCa screening method is a contentious one, as it is not felt to have the correct balance between lives saved and harm caused.

> "This could change the balance of the equation."

Currently, the screening approach begins with repeated measurements of prostate-specific antigen (PSA); if elevated PSA levels are found the next step is a transrectal ultrasound-guided random prostate biopsy (TRUS-biopsy). Typically, a fine needle is used to take 6–12 samples from the prostate. With this technique, there is a chance of discovering a small cancer that may not be clinically threatening, which could lead to unnecessary procedures due to overdiagnosis. Therefore, an improved method is of great importance.

Researchers studied outcomes in a group of heavily pre-screened men: it was acknowledged that this heavy pre-screening was a potential limitation of the study. Six TRUS-biopsy samples were taken from 177 men and 12 TRUS-biopsy samples were taken from a further 158. The 158 men in the latter group were first given an MRI scan and if the MRI scan detected a potentially suspicious area then additional MRI-targeted samples were taken. The findings suggested that while all methods had a similar detection rate for high-grade cancers, the MRI-targeted biopsy approach resulted in a significant reduction in the number of biopsies required. Overall, 70% of men did not require a biopsy and the MRI-targeted approach also saw the number who were overdiagnosed with a non-aggressive PCa cancer cut by ~50%. Looking ahead, the researchers hope their findings will provide a stepping stone for confirmatory studies to attempt to reproduce these results and garner a deeper understanding of the statistics and cost-effectiveness of the method to determine whether it could be recommended for routine use in the future.

Test to Predict Those at Greatest Prostate Cancer Risk

A GENETIC test that predicts the patients most at risk from aggressive prostate cancer (PCa) and their likelihood of treatment failure was presented at the Annual EAU Congress, as reported in a EAU press release dated 26th March 2017.

> “It also means that we can begin to look at better screening for those who are at risk, for example among those men with a family history.”

Researchers investigated the Kallikrein (KLK) region of chromosome 19 in 1,858 patients with aggressive PCa (defined as having a Gleason Score >8); they searched for small single-point inherited mutations. Their findings revealed several variants of the *KLK6* gene were associated with more aggressive PCa. Men with these gene variants were found to have a three-times greater risk of developing aggressive PCa. With these gene variants found in between 6% and 14% of men, this makes it one of the most common genes that has currently been found to be associated with aggressive PCa.

Furthermore, these inherited gene variants were found to independently predict treatment failure, based on a cohort of Canadian men from the International Cancer Genome Consortium (ICGC). Men with these gene variant mutations who had undergone radiation treatment or surgery were found to have a greater likelihood of recurrence: three-times greater than the rest of the population. The researchers noted that further sequencing studies could be of use in discerning rare variants that might have a major effect in the *KLK6* region.

Speaking about the practical benefits of this test, lead study author Dr Alexandre Zlotta, Lunenfeld–Tanenbaum Research Institute, Toronto, Ontario, Canada, elucidated: “It should mean that if you have a high prostate-specific antigen level but are unsure about having a biopsy to confirm whether you have cancer, this test could help you decide. It also means that we can begin to look at better screening for those who are at risk, for example among those men with a family history. As the test is refined we may be able to move towards more intelligent prostate screening.”

Up to 40% of Prostate Cancer Patients Left Undertreated

MEN diagnosed with locally advanced prostate cancer (PCa) in England may not always be receiving the most appropriate treatment for their condition, possibly lowering their survival rates.

The research, presented at the EAU 2017 Congress, showed that almost 4 in 10 men with this form of PCa are ‘undertreated’, most

commonly with hormonal treatments alone without additional radiotherapy or surgery. Major studies have shown that radiotherapy or surgery as well as standard hormonal treatments have improved survival rates in comparison to those patients who only receive hormones. While hormonal therapy helps to slow the growth of PCa it usually cannot completely eradicate it. In the UK alone, there were >46,000 new cases of PCa, which led to >11,000 deaths in 2014, making this an especially salient issue.

> “This study has demonstrated that in current practice many men do not have their high-risk PCa treated by radical therapy or radiotherapy and hormones.”

The research was carried out by the National Prostate Cancer Audit (NPCA), whose team analysed the first figures that have arisen from linking the NPCA to other major UK databases including but not limited to the National Cancer Data Repository. After looking at 2014–2015 records, they discovered that of the 11,957 men with locally advanced PCa, 39% were placed on hormonal treatment alone. Of the remaining 61%, 42% were treated with radiotherapy, 18% underwent surgery, and 1% received brachytherapy.

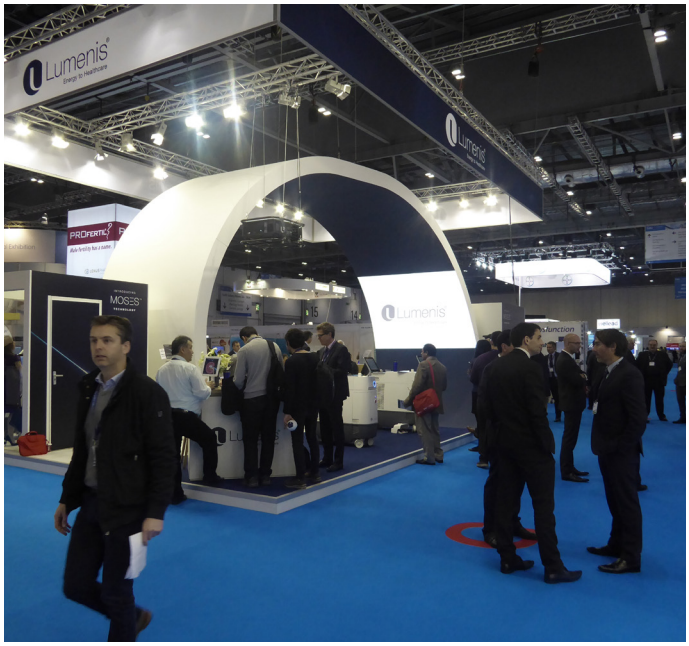
The fact that so many men with this form of prostate cancer are not benefitting from optimal treatment methods is something that needs to be explored further, according to the authors of the study.

Mr Prasanna Sooriakumaran, Urological Consultant, University College London Hospital, London, UK, commented in a EAU press release dated 26th March 2017: “This study has demonstrated that in current practice many men do not have their high-risk PCa treated by radical therapy or radiotherapy and hormones. The true reasons for this are unexplained and need further investigation to ensure that all men with this type of prostate cancer receive maximal curative therapy when it is clinically appropriate.”

Testicular Cancer Death Much More Likely Amongst People with Learning Difficulties

DEATH caused by testicular cancer is four-times more prevalent among people with learning difficulties than the general population, according to a study presented at the EAU Congress. This is stated in a EAU press release dated 27th March 2017.

Previous research has shown that people with learning difficulties die significantly earlier on average than the general population: 13 years in males and 20 years in females. The study sought to discover if there was any correlation between testicular cancer incidence and learning difficulties. Currently, testicular cancer is the third leading cause of death amongst men aged between 18 and 50 years old.



The researchers from the University of Birmingham, Birmingham, UK, analysed 158,138 male patients with learning difficulties using the NHS's Hospital Episode Statistics database, which included data from 2001–2015. Of these patients, 331 had testicular cancer and 32 died from it; this was a far higher proportion compared to the general population where 25,675 had testicular cancer and 713 passed away in the same period.

> "We found that people with learning difficulties are not only more likely to develop testicular cancer, but are also far more likely to die from it than the general population."

Commenting on the findings, lead author Dr Mehran Afshar, St George's Hospital, London, UK, stated: "We found that people with learning difficulties are not only more likely to develop testicular cancer, but are also far more likely to die from it than the general population. Testicular cancer is relatively rare, but if similar imbalances apply to all cancers, which we suspect to be the case, this would make excess cancer deaths associated with learning difficulties a significant public health issue. However, we do not yet have any statistics to confirm this. We are still processing the data on other cancers, such as prostate, breast, and colorectal cancer."

He continued: "We propose that there might be several reasons which cause this disparity in survival, perhaps including the possibility that men with learning difficulties are not so good at self-examination, going to the doctor, and then following through with any treatment. It could also be that because consent is more difficult to obtain from these patients it affects the treatment they receive."

Reducing Salt Intake Decreases Night-Time Urination

NOCTURIA, a medical term used for excessive urination at night and a condition that is common for people >60 years of age has been associated with the increased amount of salt consumption in one's diet. Researchers from the Nagasaki University, Nagasaki, Japan, have discovered that reducing the amount of salt in a person's diet can also reduce the need to urinate, for both male and female patients, during night-time sleep. This is according to a EAU press release dated 26th March 2017.

> "Here we have a useful study showing how we need to consider all influences to get the best chance of improving the symptom."

The research was led by Dr Matsuo Tomohiro, Nagasaki University, Japan, who studied 321 patients who had a high salt consumption in Japan and also had issues with sleep. Dr Tomohiro separated the study population in two, reducing 223 participants' salt intake from 10.7 to 8.0 gm/day whilst increasing the salt intake of the remaining participants (n=98) from 9.6 to 11.0 gm/day. The results showed a decrease in night-time urination from 2.3 to 1.4 times/night for the reduced salt intake group whilst those with an increased salt intake needed to urinate more frequently during the night (from 2.3 to 2.7 times/night). Similarly, those whose reduced their salt intake also urinated less frequently during the day.

Although a condition such as nocturia may seem trivial to some, the knock-on effects can be serious. Lack of sleep, for example, has been associated with problems such as stress, irritability, and general tiredness and therefore can significantly impact a patients' quality of life. Commenting on the success of the study, Prof Marcus Drake, Bristol University, Bristol, UK and Working Group Lead for the EAU Guidelines Office Initiative on Nocturia, explained: "Research generally focusses on reducing the amount of water a patient drinks, and the salt intake is generally not considered. Here we have a useful study showing how we need to consider all influences to get the best chance of improving the symptom."

Do Sleep Disorders Increase the Incidence of Night-Time Urination?

NOCTURIA, a condition that affects >50% of individuals over the age of 50, has been one of the hot topics presented at this year's EAU congress that took place in March at the ExCel Centre, London, UK. According to a EAU press release dated 26th March 2017, nocturia, the condition meaning frequent urination during the night-time, has been found to be exacerbated in individuals who are also suffering from obstructive sleep apnoea (OSA).

Currently, OSA, a condition which causes the walls of the throat to relax and narrow and therefore increases the difficulty of breathing whilst asleep, affects between 2% and 4% of the population. Both men and women are affected. Now new research presented at the EAU has demonstrated that wearing a Continuous Positive Airway Pressure (CPAP) mask, typically used to combat OSA, also reduces the frequency of night-time urination.

> "This is the first study to show the true incidence of nocturia in patients who suffer from OSA. It is also the first study to show the size of the effect of CPAP mask treatment in patients with OSA on their nocturia symptoms."

Researchers from the Maastricht University Medical Centre, Maastricht, Netherlands, treated a total of 256 patients (206 male, 50 female; mean age: 60 years [28—92]) who were already being treated for OSA with a CPAP mask. Of these patients, 31% had no symptoms of nocturia prior to or after use of the CPAP mask, whilst the remaining 69% had reported nocturia at a frequency of ≥1 void per night. The severity of nocturia prior to the study affected the results, for example, researchers reported that 32 out of the 77 patients who had reported 2 voids per night were now able to sleep undisturbed throughout the whole night whilst wearing the mask. Overall, results indicated that 65% of OSA patients with ≥1 incidences of needing to urinate at night had a reduced number of incidences after using the mask.

Dr Sajjad Rahnama'i, Maastricht University Medical Centre, Maastricht, Netherlands, who was lead researcher in the study, explained the significance of the results: "This is the first study to show the true incidence of nocturia in patients who suffer from OSA. It is also the first study to show the size of the effect of CPAP mask treatment in patients with OSA on their nocturia symptoms."

Overuse of Overactive Bladder Drug Linked to Dementia: Should we be Funding Alternatives?

OVERACTIVE bladder (OAB) has commonly been treated with oxybutynin, a drug that has been associated with dementia and cognitive impairment in elderly patients when taken orally. At the Annual EAU Congress, concerns were expressed about the lack of funding for alternative treatments in Europe, and analysis shows that oxybutynin is currently prescribed in 27.3% of all OAB cases. This was described in a EAU press release dated 27th March 2017.

As OAB is extremely common in individuals >65 years of age, initial treatment usually consists of behavioural modification. First-line medical treatment, such as antimuscarinic medications including oxybutynin, then follows. Antimuscarinic drugs have several uses, including controlling OAB, as they block the activity of muscarinic acetylcholine receptors. Although oxybutynin is linked to increased cognitive decline in elderly individuals, it is still commonly administered, typically because it is the least expensive medication for this condition.

Dr Daniel Pucheril, Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan, USA, examined evidence from the National Ambulatory Medical Care Survey. The survey showed that 1,968 patients aged >65 years had received a new antimuscarinic medication, and 27.3% of these were prescribed oxybutynin for OAB. It was recommended by the US Food and Drug Administration (FDA) that all patients starting oxybutynin should be closely monitored for adverse effects of the central nervous system, yet at the time of prescription only 9% of patients had received a neurological exam.

> “We are not saying that everyone should change from oxybutynin to another drug: it still has its uses, and coming off the drug without medical supervision is not recommended. Nevertheless, doctors need to look closely at the levels of prescribing.”

Dr Pucheril explained: “We looked at a representative sample, but when you extrapolate to the US population the figures are huge. We estimate that over the 6 years of our analysis, 47 million individuals in the USA were taking various types of antimuscarinic drugs for OAB, with around 55% of new prescriptions going to the >65s.”

He continued: “We are not saying that everyone should change from oxybutynin to another drug: it still has its uses, and coming off the drug without medical supervision is not recommended. Nevertheless, doctors need to look closely at the levels of prescribing.”

Commenting on the situation in a broader context, Prof Andrea Tubaro, Sapienza University, Rome, Italy concluded: “funders in all countries really need to support the use of a range of drugs.”

The authors believe that focus should be directed towards the identification of accessible novel treatments that do not require the level of monitoring required by oxybutynin.

Erectile Dysfunction Patients: Stem Cell Treatment May Restore Sexual Function

GROUNDBREAKING research has discovered that stem cells have the potential to restore sufficient erectile function, enabling men who had previously been impotent to have spontaneous sexual intercourse. Results from this Phase I trial need to be interpreted accordingly, as safety and dosage were the primary factors addressed in this early study. For several years, groups have researched the ways in which stem cell therapy can be developed to help cure erectile dysfunction, yet this is the first time patients who have recovered have been able to successfully engage in sexual intercourse.

The findings showed that 8 out of 21 individuals successfully regained sexual function following stem cell therapy. Lead researcher, Dr Martha Haahr, Odense University Hospital, Odense, Denmark, stated: “What we have done establishes that this technique can lead to men recovering a spontaneous erection, in other words, without the use of medicines, injections, or implants. We are now beginning a larger Phase II trial to better evaluate its effectiveness and confirm safety.”

Stem cells were taken from abdominal fat cells via liposuction. The stem cells were isolated and then injected into the corpus cavernosum area of the penis. None of the 21 participants reported significant side effects in either the trial period or the 12-month follow-up period; patients were under local anaesthetic and able to be discharged the same day.

Sexual activity was restored for 8 of the 21 patients within 6 months of treatment, and this improvement was maintained for 1 year, signalling possible long-term benefits. Erectile dysfunction was measured through the International Index of Erectile Function (IIEF) Questionnaire. All 21 individuals reported that their score had increased from 6 to 12, 6 months after the stem cell transplantation therapy. However, the 8 individuals who had their sexual function recovered reported an increased IIEF score rising from 7 to 14. A score of 25 is average for men with 'normal' sexual function. Consequently, some individuals were able to have spontaneous erections enabling penetrative sex, and others still required additional medication.

Dr Haahr shared her concluding thoughts in a EAU press release dated 25th March 2017: "This suggests the possibility of therapeutic options for patients suffering from erectile dysfunction from other causes. But we need to remember that this is a small trial, with no control group. We are still some time away from a clinically availably solution."

> "What we have done establishes that this technique can lead to men recovering a spontaneous erection, in other words, without the use of medicines, injections, or implants."

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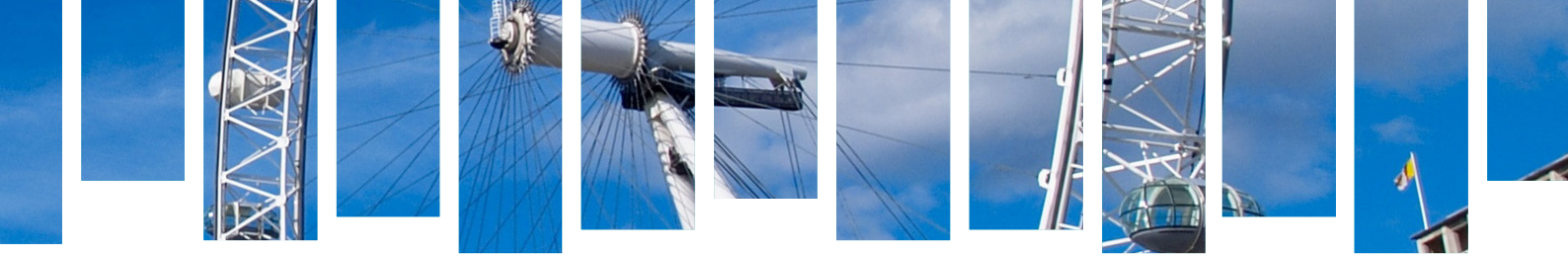


Abdullah Erdem Canda

Professor of Urology, Department of Urology, School of Medicine, Yildirim Beyazit University, Ankara Atatürk Training and Research Hospital, Ankara, Turkey.

Q: What first drew you to specialise in urology and, more specifically, robotic urology?

A: I always wanted to deal with surgery, particularly abdominal surgery, during my medical school education. Following my clinical attachment in the department of urology, I became interested in the field because you can perform both open and endoscopic surgery. Robotic urology is a high-technology surgery that very much facilitates performing complex laparoscopic, surgical, particularly uro-oncological, procedures with the use of the surgical robot; this has many advantages. We had the opportunity to use the surgical robot at our institution in Ankara, leading me to specialise in this practice.

Q: Could you tell us more about robotic urology and how it is being implemented within healthcare around Europe and globally?

A: Although it is more expensive than open or laparoscopic surgery, robotic urology is increasingly being performed around the world, including Europe, because of its many advantages. Within the private setting it is more expensive but in government institutions linked to the Ministry of Health (Turkey) it is free for cancer patients.

Q: Could you tell us about the da Vinci Surgical System; why is this so important?

A: This surgical, robotic system gives the advantages of providing three-dimensional (3D) high-definition magnified vision, the capability of using wristed hand movements and dexterity, and the ability to operate in a seated position rather than standing as in open and laparoscopic surgery. Being able to use four arms of the robot and using the camera and the fourth arm for assistance, allows the surgeon to be less dependent on the bedside assistant surgeon. Therefore you can perform complex surgical procedures easily when compared to standard laparoscopy, making the surgical robot an important high-technological device to use.

Q: In what ways does your work intersect with robotic technology on a day-to-day basis?

A: I mainly deal with surgical uro-oncology and perform robotic urology for the surgical management of prostate cancer, kidney cancer, and bladder cancer. In addition, I also perform robotic surgery for adrenal mass lesions and uretero-pelvic junction obstructions that need to be corrected surgically.

Q: More generally, what are your thoughts on the advancements in technology regarding the diagnosis and treatment of diseases? Is it something we should be encouraging more of in the future and are there any areas of concern?

A: There have been many technological advancements both in the diagnosis and treatment (medical and surgical) of diseases, including urological diseases. With the use of technology, we are now able to make the diagnosis of many urological diseases at an earlier stage, enabling us to treat the diseases earlier; this is a benefit to both the patient and physician or surgeon. Surgical management of a small and localised tumour is always easier compared to a large and advanced tumour. In addition, many genetic markers and tests are being developed that enable us to identify if an otherwise healthy patient has a significant risk factor for developing a particular cancer, and therefore if preventative measures need to be taken.

> “With the use of technology, we are now able to make the diagnosis of many urological diseases at an earlier stage, enabling us to treat the diseases earlier...”

> “Medical students and our residents take great interest in all technological developments, and robotic technology is one of the clear examples.”

Q: How have training programmes for doctors and surgeons been influenced by the advancement of robotic technology?

A: Medical students and our residents take great interest in all technological developments, and robotic technology is one of the clear examples. In robotic surgery, we teach anatomy to medical students in the operating room because they can watch the whole procedure on the screen with magnified images. This allows them to view all details clearly and if one can see the details, she/he can learn more efficiently. In terms of training our fellows in urology, robotic surgery gives a lot of advantages. As an example, our institution in Ankara is a European Association of Urology (EAU) Robotic Urology Section (ERUS)-certified robotic urology training centre and we train our own fellows and also those from other institutions. They initially observe and watch the cases that are performed and then start as a bedside assistant surgeon and proceed with hands-on training as a console surgeon. This step-wise robotic surgical training programme is easy to apply and easily trains those colleagues interested in robotic surgery as they can see many robotic surgeons' performances and different surgical techniques applied. I think that robotic surgery has made a significant impact on training.

Q: How would you like to see the use of robotics in urology expand and develop over the next few years? Where in healthcare do you think robotics will present the greatest value?

A: I think that robotic surgery will be applied more frequently in the future for the surgical management of prostate cancer, bladder cancer, and kidney cancer. With the development of smaller sized instruments, I think that it will also be used more frequently in paediatric patients.

Q: In your opinion, how important are international urology congresses such as EAU for practitioners such as yourself? Are there any sessions or presentations at this year's congress that you are particularly looking forward to?

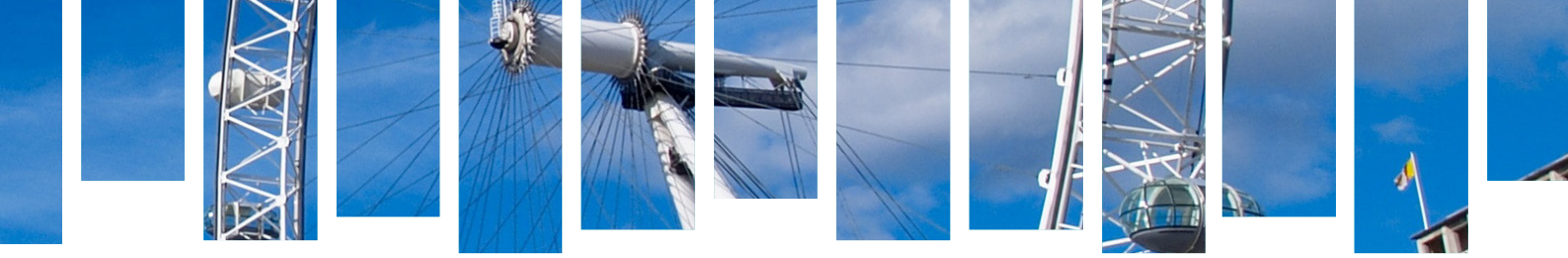
A: The EAU congress is one of the biggest urology meetings in the world, and includes many sessions, courses, live surgical procedures, and training options, therefore it is a very important event to learn the most up-to-date information and developments. Over the course of just a few days, one is able to learn lots of new information that I think is a great advantage to practicing professionals. As I am particularly interested in robotic urology, I am planning to participate in robotic urological sessions and events mostly. I will be personally taking part as a lecturer at the 'Robotic assisted radical prostatectomy - Semi-Live Masterclass, Thematic Session 18', on Monday 27th March and The European School of Urology (ESU) and ERUS Hands-on-training (HOT) courses in robotic surgery (HOT 27 & 28) on Sunday 26th March, both of which I think would be very useful for the attendees.

Q: What has been your proudest achievement so far during your medical career?

A: I think that our institution being an ERUS-certified robotic urology training centre is my proudest achievement so far in my medical career. This means that we are able to train the future generation in the field of robotic urology and will be able to pass our experience and knowledge to other colleagues. In this way, they will be able to treat many more patients and hopefully will continue the training throughout generations. This will be a strong chain of training colleagues and treating of patients, that I think will prove very important for the future.

Q: Finally, what advice would you give to aspiring medical students with an interest in robotic urology?

A: In our institution, we welcome all of our medical students to our robotic surgery operating room and explain the details of anatomy and the basics of the robotic surgical procedures that we perform. They are able to see all the details and thus are



able to learn a lot. In addition, they can ask many questions and we do our best to answer them all. We also discuss the disease of the patient. I think that this is one of the best ways of interactive learning to ensure that the knowledge is never forgotten. I suggest that medical students who are interested in robotic surgery come to visit and spend time in the operating room; this will provide very good experience.

Piotr Radziszewski

Professor of Urology and Chairman of the Department of General, Oncological, and Functional Urology, Medical University of Warsaw, Warsaw, Poland.

Q: As Professor of Urology and Chairman of the Department of General, Oncological, and Functional Urology, Medical University of Warsaw, Warsaw, Poland, what job roles and responsibilities do you have?

A: Being a chairman of one of the biggest and busiest departments in Poland is challenging. We do around 3,000 surgeries per year and see close to 5,000 patients in hospital. We cover the whole spectrum of urology, but the department's special interests are oncology, neuro-urology, and stones. I have the honour of working with fantastic people: staff members, residents, and nurses. We have created a perfect team. This allows me to work at both national and university levels. I am an advisor for the President of Poland and I chair the University Hospitals Committee within my University. Aside from that I serve the European Association of Urology (EAU) as a member of the Scientific Congress Committee.

Q: We understand that you have an interest in urological oncology and biomarkers. What initially motivated you to specialise in these areas and what particularly piqued your interest?

A: Urological oncology is an emerging subspecialty, as we have more and more registered drugs with proven influence on survival. The story started with kidney cancer, where so-called 'smart drugs' completely changed the picture of the natural course of the disease. We are now facing a true eruption of new drugs for prostate cancer (PCa) and soon this will also be true for bladder cancer, after completion of the ongoing clinical trials. But with this abundance of drugs we need to know which drug should be given to which patient. In other words, we need to personalise the treatment as much as possible by describing the signature of each individual disease. This could be achieved using different biomarkers.

Q: There are many potential clinical uses for biomarkers in the field of urological cancers, including in diagnosis, prognosis, and selection of therapy. Out of the possibilities biomarkers offer, which one excites you the most?

A: We can have diagnostic, prognostic, and therapeutic biomarkers, where the latter represent the ultimate development because they are able to indicate which patient would respond to which treatment. The biggest progress has occurred in PCa. The reasons for this are not only the huge progress in understanding PCa biology and advances in molecular and proteomic techniques, but also the increasing awareness of prostate-specific antigen (PSA) limits and perspective of its upcoming clinical withdrawal. Simultaneously with emerging prospective updates, the question about PSA replacement or its supplementation is being raised even more often. Based on current knowledge, not every described assay is eligible for population screening but most show at least interesting potential as stratifying, differentiating, and prognostic tools. Because the majority of novel tests can be implemented in clinical decision-making algorithms and thus influence both diagnosis-timing and management, the economic impact of novel biomarkers is incalculable. Although further careful validation studies are indisputably required

and novel-test screening or guidance is far from being widely available, PSA's era seems to be at its end.

Q: With the economic cost of healthcare becoming an ever-pressing concern, how can the utilisation of biomarkers assist with this issue? Do you think economic considerations will influence the clinical use of biomarkers across European countries?

A: It is not a secret that we cannot spend an unlimited amount of money on healthcare. Therefore, regulatory agencies and governments are looking for a tool to optimise the costs. One such tool could be a set of biomarkers or a single biomarker that could predict which patients will respond the best to therapy. Another biomarker could predict recurrence of the disease allowing treatment at an early phase (easier and cheaper). We can already observe a positive attitude from the regulatory authorities towards so-called companion biomarkers (biomarkers linked to a therapy or drug). A drug candidate with a biomarker linked to it is much more likely to be reimbursed than a drug without it.

Q: How important do you consider raising awareness of urological cancers amongst the public to be in terms of diagnosis? Is there any advice you would offer in this regard?

A: An early stage cancer is always better to treat and more likely to be cured. I am involved in a number of awareness campaigns in Poland. I support the patients' society 'Polish Patient' and recently we signed an agreement with the city of Warsaw for a big educational programme. Biomarkers are really advancing the screening process, especially the genetic ones, allowing screening for predisposition to inherited cancers, for instance.

> "It is not a secret that we cannot spend an unlimited amount of money on healthcare. Therefore, regulatory agencies and governments are looking for a tool to optimise the costs."

> "...when most of the information is just a few keyboard clicks away it is even more important to precisely select and verify the research."

Q: As a member of the Scientific Committee of the Polish Urological Association (PTU) and a member of the Scientific Committee of the EAU, what motivated you to become a part of these scientific committees? Do you believe that it is an important factor for the progression of urological research?

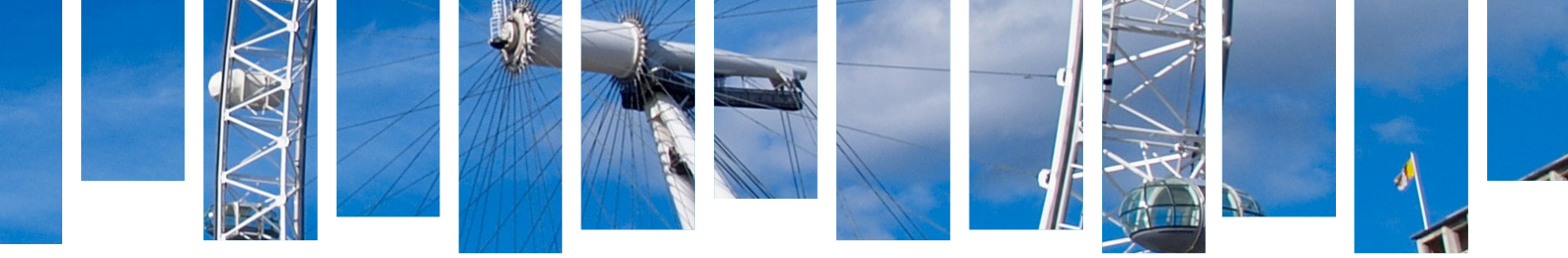
A: The scientific committee's role is to facilitate and, to a certain extent, scrutinise the demonstration of research results. Nowadays, when most of the information is just a few keyboard clicks away it is even more important to precisely select and verify the research. Twenty years ago there were two major urological events and they were covering almost all urological research in the world. Now we see more and more congresses, but not all research is initially presented during them. Therefore, it is important to familiarise the EAU members with them e.g. during the plenary and thematic sessions.

Q: Are there any technologies that you believe we should be aware of in the future that could have a positive impact on urological oncology?

A: The miniaturisation and progress of data transfer will definitely have an impact. Next generation sequencing (NGS) has already changed the field of genomic studies. The future will be the automation of the liquid biopsy (blood analysis for circulating cancer DNA) and hopefully genetic urine analysis for various biomarkers.

Q: Are there any aspects within urological oncology that you believe need more attention and how would you like to see these areas develop over the next 15 years?

A: In the future we shall cure the diseases, as opposed to merely controlling them. For sure there will be more robotics in urology, but also more focal (organ sparing) therapies. Technologies for sparing the kidney, bladder, and prostate will develop together with intelligent drug delivery to the disease site. We already witness that in PCa for example.



Q: Throughout your life, you have achieved a great deal. Which of these achievements are you most proud of and why?

A: Being a doctor, the biggest success for me is the wellbeing of my patients, it does not matter how pathetic that sounds. Little victories over the disease, the smile of a patient and his/her family is the biggest success for every one of us. After a difficult surgery when your body is pumping adrenaline, the knowledge that you did it is the biggest reward. Finally, when you know that with your research you have changed the fate of millions, that is the ultimate achievement, for which I am still waiting.

Q: Do you have any advice for aspiring urologists hoping to specialise in urological oncology?

A: Trust your patient, listen to him or her, and try to stay up-to-date with the research. Finally, train your surgical skills and do not be disappointed with small defeats, since we have all experienced them.

Christopher Chapple

Consultant Urological Surgeon, Royal Hallamshire Hospital; Honorary Professor, University of Sheffield; Visiting Professor, Sheffield Hallam University, Sheffield, UK; Secretary General, European Association of Urology (EAU).

Q: As a Consultant Urological Surgeon at the Sheffield Teaching Hospitals NHS Foundation Trust, Honorary Professor at University of Sheffield, and Visiting Professor at Sheffield Hallam University, Sheffield, UK, can you give a brief insight into your roles and responsibilities?

A: I am a Consultant Urological Surgeon employed by the National Health Service (NHS), with a special interest in functional and reconstructive urology. I am Director of Research in the Urology department and I, along with 15 consultant colleagues, provide a urological service to the population of Sheffield and its environs (1 million), and also receive subspecialist referrals from other parts of the UK and abroad. I am involved in both clinical and basic science research and in the teaching of medical students.

Q: Why in particular did the study of the functional reconstruction of the lower urinary tract and its underlying pharmacological mechanisms pique your interest?

A: Early in my career I gained experience in reconstructive urology when I trained at the Middlesex Hospital and Institute of Urology, London, UK, and found reconstructive urology fascinating as this allowed the urologist to practice urology from bench to bedside. The department at the Middlesex Hospital developed modern urodynamics as we know it, and early in my career I completed my doctorate in pharmacology and trained under some of the most eminent reconstructive urologists in the UK at that time.

Q: You recently chaired the UK male lower urinary tract symptoms (LUTS) guidelines report for the National Institute for Health and Care Excellence (NICE). In what ways are you expecting this to improve clinical practice going forward?

A: The principles behind the NICE guidelines are identical to those of the European Association of Urology (EAU) guidelines office, in that by considering the evidence underlying our clinical practice we can identify research questions which can be addressed and thus improve our clinical care. The application of the PICO approach (population, indication, comparator, and outcome) as applied to clinical questions allows us to interrogate the literature and identify the evidence base and thereby provide the highest quality clinical care for our patients. This is the approach that we use at the EAU as we have the most comprehensive and up-to-date guidelines, which form the backbone of all of our educational and research activities

at the Association. These guidelines have been endorsed by the national urological societies of all 28 European Union (EU) member states and in 27 countries outside Europe including China, Australia, and India.

Q: Across the field of urology in general, what are some of the most pressing issues that need to be addressed during 2017?

A: The most pressing questions at present within the field of urology relate to the appropriate application of the latest endoscopic and laparoscopic techniques including the use of robotic devices for carrying out surgery. Another important area is the appropriate use of drug therapy in the management of both benign and malignant urological conditions. Diseases such as prostate cancer, bladder cancer, and kidney cancer are all potentially life-threatening conditions, while disorders of the lower urinary tract have an important influence on quality of life. With the increasing age of our society we see more and more conditions such as benign prostatic hyperplasia and bladder over and underactivity that disrupt the daily lives of patients.

Q: Innovation and technological advancement within healthcare is fast becoming a topical subject of discussion across all therapeutic areas. How do you think this might influence urological diagnosis and therapy?

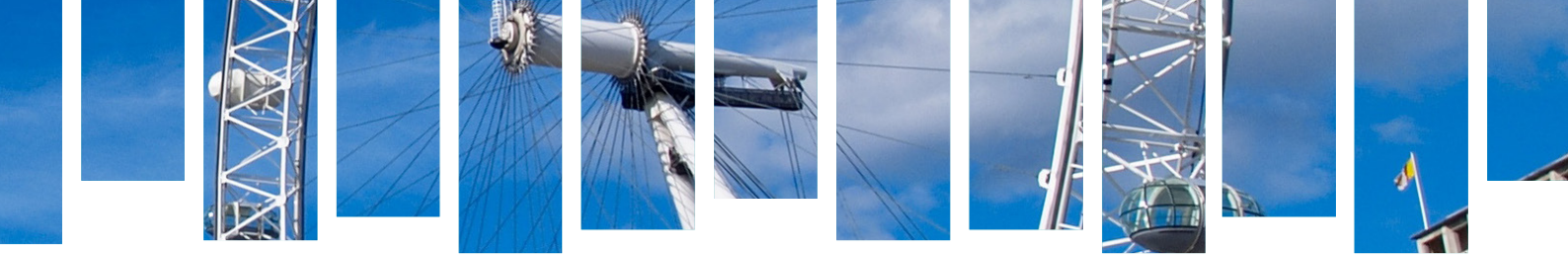
A: There have been many recent innovations and technological advancements in urology which require careful evaluation before they are introduced into clinical practice alongside appropriate monitoring of long-term outcomes. It is of fundamental importance to us as urologists to keep up-to-date with the latest developments in the field and to carefully and critically evaluate the evidence base underlying the introduction of these new therapies, which are often extremely costly, so we can ensure our patients receive the most appropriate therapy. In this context we work closely with colleagues in other specialities in a multidisciplinary fashion. We have recently been successful in obtaining approval for the establishment of a European Reference Network (ERN), eUROGEN, which aims to provide a multidisciplinary platform to deal with rare urogenital diseases and complex conditions affecting the lower urinary tract. This is subdivided into three work streams: paediatric practice; working closely with the European Society for Paediatric Urology (ESPU) and the European Society of Coloproctology (ESCP); and rare malignant conditions and rare functional disorders affecting the lower urinary tract.

Q: As Scientific Co-ordinator of the EU-funded Training Urology Scientists to develop Treatments (TRUST), can you discuss any novel treatments for overactive bladder symptoms in development that you are particularly enthusiastic about? How important will this prove within the clinic?

A: It has been increasingly recognised over the last decade that the sensory innervation of the lower urinary tract, and in particular the bladder, is the main target. The pivotal symptom of the overactive bladder symptom complex for instance is urgency, which is a compelling desire to pass urine that is difficult to defer. All of our therapies at present act primarily on sensory nerves, rather than on the bladder muscle itself, and it is recognition of this which is leading to the most appropriate development of new therapies in this field. The TRUST programme which I co-ordinated (a Marie Curie project funded by the European Commission) evaluated several novel approaches related to this and led to significant developments in our understanding of the field, as reported in the research literature.

Q: Drawing on your experience as a past Director of the European School of Urology (ESU), how important are educational platforms such as these for discussion and the sharing of expertise and knowledge among urological professionals?

A: Education is of fundamental importance, both for residents and trained urologists, along with guidelines, scientific publications in the field, the critical appraisal of new developments, hands-on training in new surgical techniques, and careful evaluation of supra specialist practice, which all come together under the banner of the ESU



to provide us with the focus for achieving one of our primary aims in the EAU, namely the enhancement and development of the best quality urological practice across Europe for the benefit of our patients.

Q: As Secretary General of Europe's biggest urological event, the EAU congress, held this year in London, UK, which aspects of the scientific programme are you most eager to attend and participate in? What advice would you give to attendees who wish to make the most of the congress?

A: It is difficult to choose as there are so many exciting additions to the scientific programme of the upcoming 32nd annual EAU congress. There will be more of a focus on personalised treatment compared to previous years. EAU17 will help delegates decide how to use the EAU Guidelines and when to judiciously individualise treatment.

This year's scientific programme will provide not only theoretical perspectives but also identify best clinical practice. It will tackle contemporary topics such as the recent evidence relating to prostate cancer screening in low-grade cancer (prospective randomised study - PROTECT), focal therapy of prostate cancer, and immunotherapy for urological cancer. The use of meshes in the treatment of urinary incontinence in women will also be analysed. This year the main plenary sessions have been expanded from four to seven to accommodate new formats such as the opening plenary session 'Sleepless nights': Would you do the same again? which critically re-evaluates management decisions in kidney cancer cases through a lawyer's perspective.

These are just a couple of the highlights in the scientific programme. The European School of Urology (ESU), as usual, introduces new innovative courses in education and highlights the latest developments in technology.

> "Apply passion and continue your interest to further develop your skills for the benefit of patients."

New additions are

- Two paediatric urology courses
- ESU Course 21 'What has changed in the non-oncology guidelines'
- ESU Course 51 'How will immunotherapy change the multidisciplinary management of urothelial bladder cancer?'
- ESU Course 45 'Oligometastatic prostate cancer'
- Furthermore, there are several new hands-on training courses including non-technical skills in urology, social media courses for both beginners and advanced users, and a course aimed for young urologists to boost their management skills

My advice is to download the EAU17 app, take a thorough look at the 5-day programme and save those sessions you wish to attend in your personal planner. For those who are not able to attend the congress in person, we are planning to report frequently via social media. Follow @uroweb via Twitter or like the EAU page on Facebook and get all #eau17 updates in an instant.

Q: Throughout your career you have strived to develop and improve the clinical care and research avenues implemented within the field of urology. What project have you been most proud to be a part of and why?

A: The training of young urologists in reconstructive urology has been my proudest achievement, although all the other aspects of my clinical practice and in particular research and the development of guidelines have also been important accomplishments to me.

Q: Finally, what advice would you give to up-and-coming clinicians or researchers with an interest in urology?

A: Be enthusiastic about the field. Apply passion and continue your interest to further develop your skills for the benefit of patients. Urology is a fascinating subject and urological problems affect >50% of the population during their lives. Using the medical and surgical treatments for the urinary tract which we have available, we can improve quality of life for many people and save many lives.

NOCTURIA: WHAT DO WE NEED TO KNOW IN 2017? IDENTIFYING THE CAUSE AND TAILORING THE TREATMENT

This satellite symposium took place on 25th March 2017 as part of the European Association of Urology (EAU) Congress in London, UK

Chairperson

Philip Van Kerrebroeck[1]

Speakers

Philip Van Kerrebroeck,[1] Marcus Drake,[2] Jonathan Rees[3]

1. Department of Urology, Maastricht University Medical Center (MUMC+), Maastricht, Netherlands
2. University of Bristol, Bristol, UK
3. Backwell and Nailsea Medical Group and Primary Care Urology Society (PCUS), Bristol, UK

Disclosure: Jonathan Rees has been an advisor and speaker for Astellas, Ferring, and Lilly. Marcus Drake has been an advisor, speaker, and researcher with Allergan, Astellas, and Ferring. Philip van Kerrebroeck has acted as advisor and speaker for Astellas, Ferring and Medtronic.
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MEETING SUMMARY

The theme of the symposium was the London tube, which is famous for the expression 'Mind the gap'; the symposium theme was tweaked to 'Mind the debate' with three debates that focussed on gaps in understanding of nocturia. Nocturia is a multifactorial medical condition with several components including nocturnal polyuria, reduced bladder capacity, and sleep disorders. Nocturia can be caused by comorbidities such as heart failure, diabetes mellitus, and sleep apnoea. The debate discussed that nocturia is a highly prevalent medical condition that increases with age and affects both men and women. Nocturia disturbs sleep and can seriously affect a patient's quality of life. The condition also increases mortality by making patients more prone to falls and to fracture the head of the femur. Nocturia results in poor concentration at work and can lead to a loss of productivity. Assessments for nocturia were considered including frequency volume charts (FVC), urine albumin to creatinine ratios, peripheral oedema examinations, bladder diaries, and ultrasound testing. One treatment for nocturia has been desmopressin, but the risks of hyponatraemia have led to a reluctance to prescribe, especially in populations aged >65 years, who are at particular risk if treated with too high a dose. Recently NOCDURNA®, a gender-specific low-dose oral lyophylisate formulation of desmopressin, has been developed (50 µg/day in men and 25 µg/day in women). At these low doses desmopressin was shown to be effective and well-tolerated in two Phase III trials and to provide rapid and sustained improvements in nocturia and quality of life. The formulation is suitable for individuals >65 years old, but the advice is that they require sodium monitoring before initiating the treatment, in the first week of treatment (4-8 days) and again at one month after treatment initiation.

Introduction

The symposium involved three debates focussing on gaps in the understanding of nocturia: 'Nocturia: why bother?', 'Is treating nocturia easy?', and 'Are all desmopressin formulations the same?'. Prof Philip Van Kerrebroeck, the chairman, outlined the evening's format with experts providing medical evidence and sharing perceptions of nocturia.

Nocturia: Why Bother?

Doctor Jonathan Rees

Nocturia can be considered a disease of ageing because it becomes more prevalent with age in both men and women. A systematic review and meta-analysis showed 'having to wake at night ≥1 times to void' affected around 55% of men aged 50–59 years, 70% aged 60–69 years, and >80% aged 80–90 years. Similarly, the analysis showed nocturia affected around 60% of women aged 50–59 years, 70% aged 60–69 years, and 80% aged 80–90 years.[1] See Figure 1.

While nocturia can be considered a normal aspect of ageing, clinicians should be careful not to 'over normalise' the condition. Short times to first void, said Dr Rees, have been associated with lower sleep quality. A study of 757 nocturia patients showed those in the lowest quartile of time to first void (<1.17 hours) were nearly three-times more likely to have Pittsburgh Sleep Quality Index (PSQI) scores indicating poor sleep (>5) than those in the highest quartile (>2.5 hours) (odds ratio [OR]: 2.96; 95% confidence interval [CI]: 1.75–5.01).[2] Furthermore, two studies showed the number of patients reporting good sleep quality decreases in direct relation to increasing numbers of nocturnal voids.[3,4] Generally, explained Dr Rees, restorative slow wave sleep occurs when people first go to sleep, making disrupted sleep in the first 4 hours the most detrimental.

Nocturia can impair quality of life, with effects including impaired daytime activity and work productivity (daytime fatigue, poor concentration, reduced performance at work, and increased sick leave) and reduced quality of life (daytime fatigue, lower perceived health, and depression).[3,5] Furthermore, nocturia has been shown to increase cardiovascular disease (CVD), falls and fractures, depression, diabetes, and obesity.[6]

The burden of nocturia increases with frequency of voids. A study showed deterioration of health-related quality of life was associated with an increasing number of night-time voids ($p<0.001$) with significant differences observed between 0–1 voids and >2 voids ($p<0.001$).[7] A meta-analysis of seven studies (N=28,220 patients) showed nocturia was associated with increased all-cause mortality (hazard ratio [HR]: 1.23 for all patients with nocturia; HR: 1.46 for patients with >3 voids).[8]

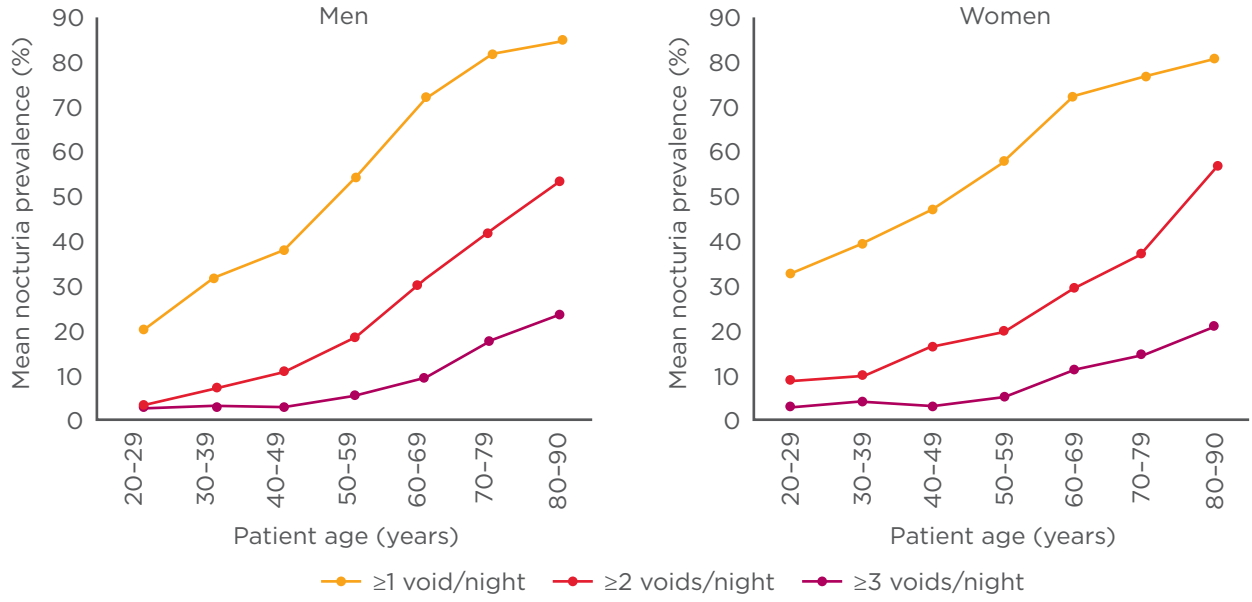

Figure 1: Nocturia is common across all age groups in both men and women.
Adapted from Cornu et al.[1]

Fatigue due to nocturia results in poor concentration at work. An analysis by Prof Van Kerrebroeck across 15 EU countries estimated the total cost of nocturia per annum due to lost productivity was around €30 billion.[9] Increased mortality from nocturia was driven by the increased risk of fractured neck of the femur in elderly patients getting up at night. Dr Rees concluded the data were clear that nocturia represents a significant health problem and that it was important for clinicians to be 'bothered' by it.

In the accompanying debate, the panel agreed that important factors urologists should take into consideration included the number of episodes of nocturia experienced each night, the timing of the episodes, and the extent to which symptoms bothered patients. What really mattered for patients, it was felt, was whether the condition disturbed their sleep. Getting up twice in the night was generally felt to be the point at which disruption started to impair quality of life. Additionally, single episodes of nocturia had greater adverse effects if they occurred in the first 4 hours of sleep (where slow wave restorative sleep occurs) as opposed to the second 4 hours. Comorbidities that may be uncovered by nocturia include CVD, undiagnosed sleep apnoea, and diabetes. There was also evidence that patients with nocturia are at increased risk from falls, fractures, and mortality. In patients presenting with nocturia, Dr Rees stressed that urologists needed to take into consideration whether they were frail and at risk from falls.

While the audience reported transurethral resection of the prostate had been largely abandoned as the principal treatment for nocturia, the panel said that the procedure is still offered at some centres and general practitioners (GPs) still refer patients. Assessments offered to nocturia patients include FVC, basic blood tests, haemoglobin A1c (HbA1c) tests, renal function, urine albumin to creatinine ratios, blood pressure tests, and peripheral oedema examinations. While FVC provide valuable information, they can be cumbersome and can take ≤3 days to perform. It was felt that more GPs would be willing to offer such tests if they appreciated that even 1 day of monitoring provides valuable information. Sufficient time also needs to be spent explaining to patients how instructive the data can be. While recording drink volumes was largely unnecessary, Prof Van Kerrebroeck felt it was important to investigate why patients with very high urinary outputs were drinking excessively, as this might impact on therapy.

Is Treating Nocturia Easy?

Professor Marcus Drake

Nocturia can be considered a multifactorial medical condition with components including nocturnal polyuria, global polyuria, reduced bladder capacity, and sleep disorders (Figure 2).

Nocturia is primarily caused by nocturnal polyuria. One study demonstrated that 76% of subjects in a European cohort of 846 nocturia patients and 88% of subjects in a USA/Canadian cohort of 917 nocturia patients experienced nocturnal polyuria.[10] Investigations to classify patients into the correct nocturia category include reviewing past medical histories; 3-day FVC; sleep questionnaires; fluid intake recordings; health-related quality of life questionnaires; and urine analysis, culture, and cytology.[11] Fluid intakes need to be taken into particular consideration for patients with kidney stones or cystitis and those who exercise intensively, as both groups drink large amounts of water. FVC used to collect quantitative voiding data offer an essential evaluation tool for classifying nocturia. Global polyuria is defined as 24-hour urinary output that exceeds >40 mL/kg body weight while nocturnal polyuria is defined as >20% of daily urine output at night in young patients and >33% in elderly patients.[12]

The European Association of Urology (EAU) Non-neurogenic Male lower urinary tract (LUTS) Guideline Panel is working to develop a sensible approach that pulls 'everything together'.[13] Their guideline for evaluation includes history (including an assessment of sexual function), symptom score questionnaires, physical examinations, urinalysis, prostate-specific antigen (if prostate cancer diagnosis changes management), and measurement of post-void residual. In addition, said Prof Drake, ultrasound of the urinary tract may be needed to evaluate hydronephrosis and post-void residuals, and bladder diaries should be considered for patients with 'bothersome' nocturia. Patients with nocturia that is not 'bothersome' should still be assessed because this offers the chance to pick up other medical conditions at an early stage. He stressed that people with comorbidities, such as heart failure, should then be steered to appropriate specialists.

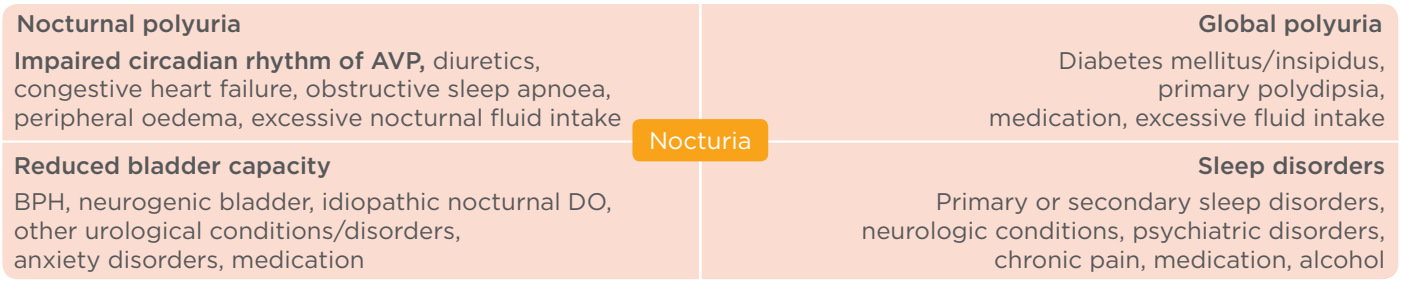

Figure 2: Nocturia is a multifactorial medical condition.[6,11]
AVP: arginine vasopressin; BPH: benign prostatic hyperplasia; DO: detrusor overactivity.

Management can then be tailored depending on the aetiology of nocturia:[11,14]

- Nocturnal polyuria: patients can be advised to reduce fluid intakes, be prescribed therapy for specific medical conditions, be prescribed desmopressin, and advised to change the time they take diuretics.
- Global polyuria: patients can be advised to reduce fluid intakes and be treated for diabetes mellitus/insipidus.
- Reduced bladder capacity patients can receive therapy for overactive bladder/benign prostatic hyperplasia and other urological conditions.

In nocturia treatment, little response has been seen for anticholinergic agents and α-blockers, Prof Drake cautioned. One study involving 997 patients with nocturia due to nocturnal polyuria found no significant difference in the number of nocturia episodes from baseline in those treated with the anticholinergic agent solifenacin 10 mg (n=400), solifenacin 5 mg (n=211), and placebo (n=386).[15] Furthermore, in a Malaysian study involving 41 patients, 85% of patients with nocturnal polyuria were unresponsive to α1-blocker treatment compared to 10% with global polyuria and 5% with normal nocturnal outputs.[16]

In the accompanying debate, the panel considered whether patients with nocturia can be effectively treated with an α-blocker and/or an anticholinergic agent. Since nocturia can be caused by a combination of storage lower tract symptoms and bladder outflow obstruction, Dr Rees felt patients with mixed symptoms would respond to α-blockers while those with storage problems would respond to anticholinergic agents. Evidence from the COMBAT[17] and STAR[18] studies, he added, showed α-blockers used in combination with anticholinergic agents produced statistically significant improvements in nocturia. Concerns were expressed that initiating combination treatments together might make it difficult to identify which drug caused side effects. Instead, Dr Rees said, he preferred to start in a 'step-wise fashion' targeting the most prominent symptom first. Bladder diaries, where patients score each void, can provide valuable information to decide whether patients might respond to anticholinergic agents. Patients with 80 mL nocturia voids with symptom scores of 3 were felt to provide the perfect candidates for anticholinergic agents taken before bed.

The audience agreed diuretic treatments in male patients with significant nocturia should be considered a waste of time and money. While national UK guidelines advise loop diuretics for nocturnal polyuria,[19-21] none of the panel recalled seeing any patients who had responded. An added complication was that, in addition to nocturia, patients receiving diuretics experienced evening diuresis. The current approach to nocturia assessment, involving multiple appointments, leads to delays of around 1 year before patients receive treatment. To prevent patients from becoming disillusioned, Prof Drake suggested that primary care was the most appropriate place to start α-blockers.

Are All Desmopressin Formulations the Same?

Professor Phillip Van Kerrebroeck

Recently a gender-specific low-dose melt formulation of desmopressin has been developed. Prof Phillip Van Kerrebroeck explained that the lower dose for female patients was because women are more sensitive to antidiuretic treatments than men and can be treated as effectively on the lower dose.[22,23]

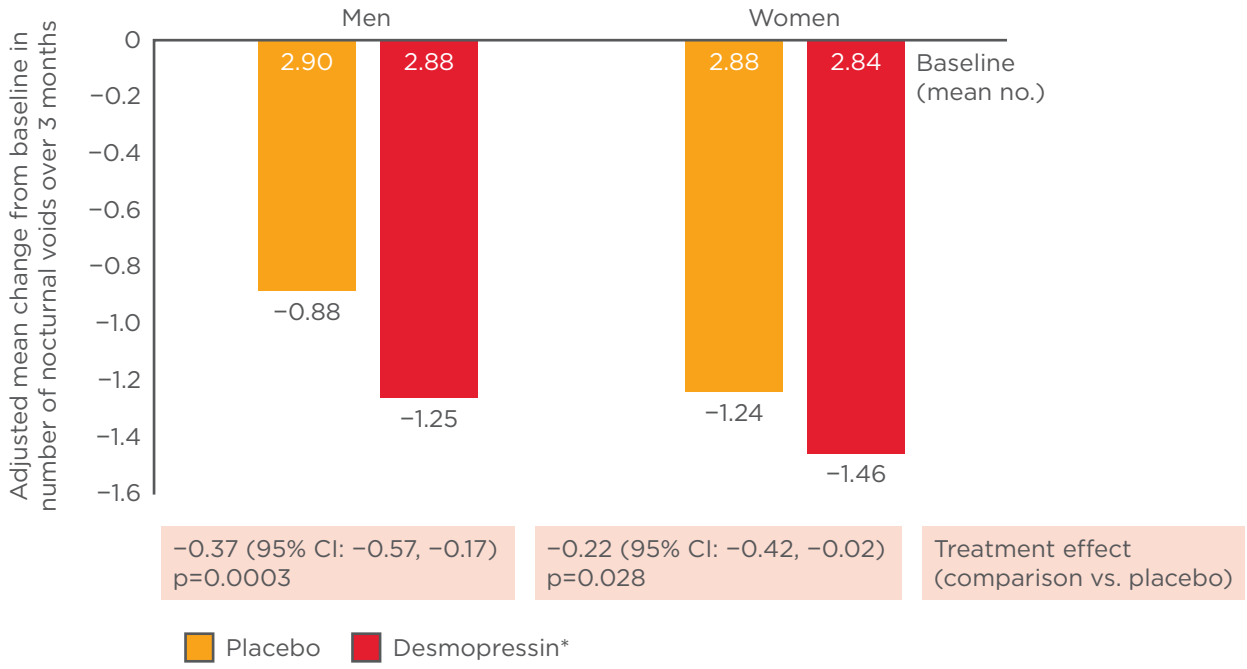

Figure 3: Significant reductions in number of nocturnal voids with low-dose desmopressin.[23,24]
*Men: 50 µg; women: 25 µg.
CI: confidence interval.

Studies in the USA and Canada showed that desmopressin 25 µg in women significantly reduced the mean number of nocturnal voids compared to placebo (p=0.028);[23] and that desmopressin 50 µg in men significantly reduced the number of nocturnal voids compared to placebo (p<0.001).[24] See Figure 3.

In women, desmopressin 25 µg increased the time to first nocturnal void by 49 minutes compared to placebo (p=0.003),[23] while in men desmopressin 50 µg increased time to first nocturnal void by approximately 40 minutes compared to placebo (p=0.006).[24]

The first period of uninterrupted sleep is important, explained Prof Van Kerrebroeck, because it correlates with feeling well rested. This view was enforced by studies showing significant increases in health-related quality of life after 3 months treatment.[23,24] Low-dose desmopressin was well-tolerated, with only two women[23] and three men[24] having adverse effects leading to discontinuation. Furthermore, only 2% of women and 2% of men experienced serum sodium levels <130 mmol/L.[23,24]

The authors of a recent meta-analysis of low-dose desmopressin studies recommended monitoring at Week 1 and additional monitoring at Month 1 for those at elevated risk (aged >65 or receiving concomitant medication associated with hyponatraemia).[25] Furthermore, the product characteristics summary for NOCDURNA® points out that for elderly patients, serum sodium must be in the normal range before initiating treatment and checked at 4–8 days and Month 1.[26] Low-dose desmopressin, concluded Prof Van Kerrebroeck, provides a good balance between efficacy and side effects (in particular hyponatraemia) and offers a welcome addition to the nocturia therapeutic armamentarium.

High-dose desmopressin, the panel acknowledged in the accompanying debate, could have significant health implications for patients with low sodium levels (<130 mmol/L). The reason UK guidelines recommend trials of loop diuretics,[19-21] said Dr Rees, is that experts have not considered high-dose desmopressin to be "safe and viable", with risks especially pronounced for older patients. The introduction of new formulations of lower-dose gender-specific desmopressin (50 µg for men and 25 µg for women) significantly reduces the risk of hyponatremia compared with higher doses.

Since risks of hyponatraemia are greatest in patients aged >65 years, the panel felt it should be considered obligatory to investigate serum sodium in this age group before starting desmopressin. Levels should then be tested again after 7 days.

If there are no major changes in the patient's medical condition there is no need for chronic monitoring, although tests should be repeated if the dose of desmopressin is changed. Patients and their relatives need to be warned that sodium should be measured if they become acutely unwell. When prescribing to elderly patients with significant comorbidities, Prof Van Kerrebroeck suggested it was helpful to involve geriatricians. Sublingual preparations, commented Prof Drake, can represent an advantage for nocturia patients since they reduce liquid consumption at bed time. Patients should also be provided with advice to maintain stable diets that do not involve reduced sodium intakes and not to increase fluid intakes. Even with the new formulations, it was felt, the advice should be to limit fluid intakes to 500 mL for an hour before bed.

Conclusion

The symposium considered how nocturia, a highly prevalent medical condition, disturbs sleep, adversely affects quality of life, and increases mortality by making patients more prone to falls. Additionally, comorbidities that may be uncovered by nocturia include CVD, sleep apnoea, and diabetes. For nocturia treatment, limited response has been seen for anticholinergic agents and α-blockers, and, while more effective, there have been concerns high dose desmopressin may be associated with hyponatraemia. Recently, new gender-specific formulations of low dose desmopressin (50 µg/ day in men and 25 µg in women) have been developed to overcome issues with hyponatraemia. The new formulations have been shown to be effective in two Phase III clinical trials.

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MELANOMA CELL ADHESION MOLECULE SUPPORTS THE AGGRESSIVE PHENOTYPE IN HUMAN PROSTATE CANCER

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Keywords: Prostate cancer (PCa), melanoma cell adhesion molecule (MCAM), bone metastasis, bone marrow/bone-specific response.

Prostate cancer (PCa) is the most common cancer in males and the second leading cause of death from cancer in men.[1] When PCa progresses from localised disease to castration resistance, the formation of incurable metastases, primarily in the bone, is almost inevitable. Therefore, understanding the factors that regulate homing and survival of metastatic cancer cells in the bone is important for the identification of new therapeutic targets.

The focus of our research is to elucidate and characterise the biological mechanisms that support PCa progression and promote the formation of metastasis. In previous work from our laboratory, Özdemir et al.[2] described the molecular signature of the bone marrow/bone-specific response in PCa-induced osteoblastic bone metastasis. This study led to the identification of several factors that reinforced the establishment of the bone metastatic niche and that might represent innovative therapeutic targets and biomarkers in osteoblastic bone metastasis.

Importantly, although in PCa the bone lesions are typically osteoblastic, in many patients osteoblastic and osteolytic lesions coexist.[3] Therefore, the objective of our current work is to characterise the subset of molecules that have a biological impact on the establishment of a common blastic and lytic bone marrow/bone-specific response.

Among these factors, our group previously identified melanoma cell adhesion molecule (MCAM) in the stroma of lytic and blastic lesions in preclinical models of PCa bone metastasis.[2] MCAM is an adhesion molecule involved in cell-cell and cell-matrix interactions and can interact with other MCAM molecules (homophilic binding) or other ligands (heterophilic binding).[4,5]

Based on this notion, we knocked down the expression of MCAM on lytic and blastic human PCa cells in order to study its biological function *in vitro* and *in vivo*. MCAM knockdown reduced proliferation in PC-3M-Pro4 Luc2 tdTomato PCa cells and resulted in increased E-cadherin expression, which suggests that MCAM may be involved in the maintenance of a mesenchymal phenotype. It has been described how metastatic human PCa cells target the haematopoietic stem cell niche in the bone marrow at the level of an 'endosteal'/'osteoblast' niche and a 'vascular'/'perivascular' niche, as reviewed by Hensel and Thalmann.[3] Therefore, we set up an *in vitro* model of an osteoblast niche[6] to study the behaviour of PCa cells upon co-culture with osteoblasts and to measure the resulting effects on cancer stem/progenitor-like markers. We found that MCAM is required for the osteoblast-mediated induction of the metastasis-initiating marker aldehyde dehydrogenase (ALDH)[7] on PCa cells. Moreover, MCAM knockdown prevented the increase in the size of the $ALDH^{high}$ subpopulation in PC-3M-Pro4 Luc2 tdTomato, mediated by human osteoblasts and prevented the establishment of bone metastasis in an intra-osseous animal model.

In conclusion, our data underscore the importance of MCAM in the maintenance of PCa bone metastasis and demonstrate that MCAM plays an important role when PCa cells localise in the bone. Altogether, MCAM appears to be a promising molecule to target the bone metastatic cascade in human PCa.

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EVALUATION OF *EX VIVO* AND *IN VIVO* BIOMARKERS IN DIFFERENT STAGES OF PROSTATIC CANCER

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Citation: EMJ Urol. 2017;5[1]:39-40. Abstract Review No. AR2.

Keywords: Prostate cancer (PCa), *ex vivo* and *in vivo* biomarkers, circulating tumour cells.

Advances in the understanding of prostate cancer (PCa) biology have led to the development of several new agents targeting different aspects of the malignant process which have been shown to prolong life. Clinical factors such as prostate-specific antigen (PSA) and pathological factors such as Gleason grading and tumour, node, and metastasis (TNM) staging are well known as prognostic markers in PCa. These tools are often insufficient for an accurate risk stratification of each patient. Therefore, it is essential for therapy monitoring to provide qualified surrogate biomarkers for survival, the ability to characterise the changing biology of the tumour at the patient's level, and qualified predictive biomarkers that can guide treatment selection based profiles derived from individual characterisation. Therefore, the detection of circulating tumour cells (CTCs) in the blood of patients with PCa might, in addition to their prognostic value, serve as liquid biopsy complementing or replacing PSA determination in predicting and monitoring the response to different therapies.[1]

We present data from a pilot study comparing different biomarkers. The CTCs represent the *in vivo* biomarker which were isolated by the CellCollector® (GILUPI, Potsdam, Germany) from the peripheral venous blood. The multiplex assay was used for the determination of the *ex vivo* biomarkers: human epidermal growth factor receptor 2 (HER-2), interleukin (IL)-6, IL-8, leptin, urokinase plasminogen activator (uPA), and uPA receptor (uPAR) were measured in serum samples.

We enrolled 34 PCa patients, 21 with localised (PCa-l) and 13 with metastasised prostate cancer (PCa-m). At multiple periods throughout the treatment, CTCs and a Luminex® assay were determined. The CellCollector was inserted in a cubital vein for 30 minutes. The interaction of target CTCs with the CellCollector was mediated by an antibody to the epithelial cell adhesion molecule (EpCAM). Captured CTCs were identified based on histological

cell architecture by immunofluorescence staining using cytokeratin (8, 18, 19), positive nuclear Hoechst staining, as well as CD45 negative staining as criteria to exclude EpCAM positive leukocytes. The Luminex assay is a bead-based principle which requires a small sample volume (≤50 µL) for the determination. All analytes could be simultaneously detected.

The baseline characteristics such as BMI, age, and smoking status were similar in all patients. The number of *in vivo* captured CTC in PCa-m patients varied from 0–820, with a mean of 17.9 CTCs and a median of 5, and in PCa-l patients the number ranged from 0–8 CTCs, with a mean of 1.6 CTCs and median of 0 was reported (Figure 1a). The CTC count, the PSA level, and the Gleason grading were significantly different in our two groups. The leptin level showed a significant difference between the two groups. In the levels of HER-2, IL-6, IL-8, uPA, and uPAR no significant differences appeared. Interestingly, significant correlations between PSA and uPAR r=0.401**; HER-2 r=0.523**; IL-8 r=0.49***; uPA r=0.324**; leptin r=-0.286**; IL-6 r=-0.298** in PCa-m patients were demonstrated. Unfortunately, the CTC numbers showed no correlation between the *ex vivo* biomarkers. The overall survival for metastasised patients with <5 CTCs was significantly (p<0.031) better than for patients with ≥5 CTCs (Figure 1b). Some personalised marker profiles of the patients displayed a correlation between the *ex vivo* and *in vivo* biomarkers (Figure 2).

The *in vivo* captured CTCs appeared to be a useful prognostic marker because the survival rate of patients with <5 CTCs was significantly better. These results confirmed the prognostic and predictive value of overall survival.[2,3] However, it is important that issues related to sensitivity and enumeration without functional characterisation of the captured cells may limit the generalisability of the assay.[4] Although there was no general validity, single patient analyses showed several, partly significant correlations between CTC count, PSA level, and *ex vivo* parameters; therefore, these markers could be useful in individual risk stratification and therapeutic decision-making.

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AN ALTERNATIVE THERAPY FOR ACUTE UNCOMPLICATED CYSTITIS

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INTRODUCTION

Acute uncomplicated cystitis (AUC) in female patients is a common diagnosis and is effectively considered as an indication for the prescription of antibiotics. The purpose of this study was to evaluate the efficiency of a non-antibacterial treatment for AUC in female patients.

MATERIAL AND METHODS

In a pilot, open, non-comparable prospective study, 17 women from the age of 18–28 years (22.4±3.6) were enrolled. The criteria for inclusion were: a diagnosis of AUC, non-pregnant sexually active women at reproductive age using optimal contraception, agreement to participate in the study, and a record

of visiting a doctor 12 hours from the beginning of the disease. The excluding criteria were using a condom/spermicide only, menopause, taking a dose of any antibiotic for any reason during the 10 days before study participation, symptoms of pyelonephritis, any complicating factors, and the duration of the disease being >12 hours.

All patients received the non-steroidal anti-inflammatory drug ketoprofen 100 mg once a day for 5 days and Canephron® N in sugar-coated pill form three times a day for 1 month. Control visits were at Day 2, Day 7, and Month 1. Results of the alternative non-antibacterial therapy for AUC were classified into the following categories: i) cured; ii) significant improvement; iii) no result; iv) worsening. Patients were followed-up after 6 months to evaluate the frequency of relapses.

RESULTS

In three patients (17.6%), symptoms had no tendency to improve after 2 days of the therapy, so antibiotics were prescribed to them and they were excluded from the study. The remaining 14 patients showed an improvement in their symptoms and continued the therapy with ketoprofen and Canephron N only. By Day 7, 12 patients (85.7%) had no dysuria or leucocyturia; this was the reason for considering them cured. Two patients (14.3%) showed insignificant dysuria and leucocyturia; because of their residual symptoms, they were considered as having shown significant improvement. All 14 patients continued the intake of Canephron N to prevent a relapse. A month later at the end of the course of Canephron N, all patients were healthy and considered to be cured. At 6 months, no relapses were diagnosed.

CONCLUSION

Non-antibacterial therapy in combination with a non-steroidal anti-inflammatory and the phytodrug Canephron N was effective for AUC in 82.4% of the final cohort: in 85.7%, it showed a good result (cured), and in 14.3% there was significant improvement. There were no relapses after using this therapy.

LONG-TERM OUTCOME OF URETEROLYSIS AND OMENTAL WRAPPING FOR IDIOPATHIC RETROPERITONEAL FIBROSIS

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Citation: EMJ Urol. 2017;5[1]:41-42. Abstract Review No. AR4.

Keywords: Retroperitoneal fibrosis (RPF), ureteral obstruction, ureterolysis, omental wrapping, renal function.

Retroperitoneal fibrosis (RPF) is a rare fibroblastic inflammatory process that involves the retroperitoneum over the lower four lumbar vertebrae and entraps one or both ureters.[1] One hundred years after the first description by Albarran, the treatment of choice for RPF-induced ureteral obstruction is still a matter of debate. This may be explained by the rarity of the disease and the different pathological subtypes.[1] The aim of the treatment is to preserve renal function and to keep patients free of stents.[2] We evaluated the long term functional outcome of ureterolysis and omental wrapping (UOR) for idiopathic RPF. Twenty-one patients (17 males and 4 females) were treated by UOR. After a median of 25 (interquartile range: 12–125) months, there were statistically insignificant changes in serum creatinine and estimated glomerular filtration rate (p=0.5 and 0.9, respectively). Renal function remained stable or improved in 12 (57%) of cases. Nine (21.4%) renal units still harboured double J stents. Preoperative hydronephrosis improved or stabilised in 90% of renal units. Intraoperative complications had been inflected in 5 (23.8%) patients and included ureteral injury, inferior vena cava injury, and duodenal

serosal injury in 3 patients, 1 patient, and 1 patient, respectively. All were managed intraoperatively with no postoperative sequelae. In conclusion, UOR has a good long-term renal function outcome as it avoids internal ureteral stent fixation in 78.6% of renal units.

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A PROSPECTIVE ANALYSIS CONCERNING THE SAFETY OF OMITTING ANTIBIOTIC PROPHYLAXIS IN TRANSURETHRAL RESECTION OF PROSTATE PATIENTS WITHOUT PREOPERATIVE BACTERIURIA/CATHETER

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Citation: EMJ Urol. 2017;5[1]:42-43. Abstract Review No. AR5.

Keywords: Transurethral resection of prostate (TURP), antibiotics (ABs), microbial resistance, bacteriuria.

INTRODUCTION

The use of antibiotic (AB) prophylaxis to reduce bacteriuria/bacteremia and clinical infectious symptoms is recommended by the European Association of Urology (EAU) and American Urological Association (AUA) guidelines (Level 1A evidence). The guidelines however are mainly based on three articles published from 2002–2005.[1-3] We currently face the problem of increasing microbial resistance and changing health economics, which requires a more cautious approach concerning AB use. We evaluated the current clinical benefit of AB prophylaxis in patients undergoing transurethral resection of the prostate (TURP) without preoperative bacteriuria/catheter and the extent of microbial resistance in our centre.

MATERIAL AND METHODS

In our study, 506 consecutive patients undergoing TURP from August 2008–September 2015 were prospectively reviewed. Only patients with a preoperative catheter/bacteriuria received AB prophylaxis. Urine analysis (preoperative, at discharge, and 3 weeks post-operation) was performed simultaneously to the analysis of the blood culture/irrigation fluid and resected prostatic tissue. All patients followed a regular follow-up protocol and all symptomatic infections were adequately treated by antibiogram.

RESULTS

Upon analysis, it was found that 67 out of 506 (13.2%) patients received prophylactic ABs, with 13 out of those 67 (19.4%) patients having had significant, asymptomatic preoperative bacteriuria and 54 out of 67 (80.6%) a preoperative catheter. Of this population, 60 out of 67 (89.5%) patients received ciprofloxacine, 4 out of 67 (5.9%) patients received amoxicillin, and 3 out of 67 (4.5%) patients received meropenem. The most common bacteria found were *Escherichia coli* (30.4%) and *Enterococcus faecalis* (19.5%). Fluoroquinolone-resistance (FQ-R) was observed in 64.2% in *E. coli*. Out of 506 patients, 8 (1.6%) had fever during hospitalisation and 1 out of 506 (0.2%) had urinary sepsis. Of the patients who received prophylactic AB, 3 out of 8 (37.5%) had fever and 10 out of 506 (1.8%) patients had fever at home, with 3 patients requiring re-hospitalisation (0.6%). Prostate tissue culture showed a significant infection in 37 out of

506 (7.3%) patients with *E. faecalis* (37.8%) and *Staphylococcus* (16.2%) as the main pathogens; FQ-R was 100% in *E. coli*. Of the cohort, 31 out of 506 (6.1%) patients had significant bacteremia with *E. coli* (19.4%) and non-haemolytic *Streptococcus* (19.4%) as the main pathogens; FQ-R was 50% in *E. coli*. Significant infection of the irrigation fluid was seen in 24 out of 506 (4.7%) patients, with the causal pathogens *E. faecalis* (25%) and *E. coli* (29.2%); FQ-R was 85.7% in *E. coli*. At the time of discharge, 35 out of 506 (6.9%) patients had significant bacteriuria, with the main pathogens *E. coli* (27.8%) and *E. faecalis* (22.2%); FQ-R was 60% in *E. coli*. Of the total patients monitored, 36 out of 506 (7.1%) had significant bacteriuria 3 weeks post-operation with *E. coli* as a causal pathogen in 36.1% and *E. faecalis* in 44.4%; FQ-R was 53.8% in *E. coli*.

CONCLUSION

Our data has shown a low symptomatic, infectious complication rate after TURP without AB prophylaxis (16 out of 506 [3.1%]), suggesting AB prophylaxis can be safely omitted in patients without preoperative bacteriuria/catheter. A new prospective randomised control trial in five centres has already been started to confirm our findings. Bacteremia, postoperative bacteriuria, and positive prostatic tissue/irrigation fluid cultures were of limited clinical relevance in our study. We believe that only symptomatic, clinical infectious symptoms should be treated. We also observed a high rate of FQ-R in *E. coli* in our population, which is a warning sign and shows that FQs are not the most suitable AB prophylaxis.

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IMPACT OF VESOMNI™ ON QUALITY OF LIFE OF MEN WITH LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA IN ROUTINE CLINICAL PRACTICE: INTERIM RESULTS FROM THE EUROPA STUDY

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Keywords: Lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH), quality of life (QoL), antimuscarinic, alpha-blocker.

Lower urinary tract symptoms (LUTS) affect ~44% of males worldwide[1] and can negatively impact

quality of life (QoL).[2] Inadequate response with monotherapy can occur in up to two-thirds of men with LUTS and often requires add-on therapy (e.g. antimuscarinic drug);[3] however, treatment with add-on therapy has not been established in routine clinical practice. Vesomni™ is a fixed-dose combination tablet containing 6.0 mg solifenacin (antimuscarinic) and 0.4 mg tamsulosin (alpha-blocker) used to treat LUTS associated with benign prostatic hyperplasia (LUTS/BPH). EUROPA is a 1-year observational study evaluating the impact of Vesomni on QoL and treatment satisfaction in routine clinical practice.

Men with LUTS/BPH who were not adequately responding to monotherapy and who were prescribed Vesomni in routine clinical practice were enrolled in ~59 sites throughout Belgium, Czech Republic, Portugal, Slovenia, Spain, and the UK. Clinical findings, medications for LUTS/BPH, and treatment-emergent adverse events (TEAEs) were collected for 1 year before and after Vesomni was prescribed. Patient-reported outcomes included the Overactive Bladder Questionnaire (OAB-q), International Prostate Symptom Score (IPSS), treatment satisfaction visual analog scale (TS-VAS), and European QoL Five Dimensions Questionnaire (EQ-5D-5L). These were recorded at baseline (Visit 1), Weeks 4–8 (Visit 2), and Weeks 9–18 (Visit 3). The primary endpoint was the change from baseline in symptom bother, measured by OAB-q (0=no bother; 100=very great deal of bother). Key secondary endpoints included change from baseline in total and coping, concern, sleep, and social interaction subscale scores of the OAB-q (0=very great deal of bother; 100=no bother), treatment satisfaction via the TS-VAS (0=not at all satisfied, 100=completely satisfied), total IPSS (0=no symptoms; 35=most severe symptoms), IPSS QoL (0=delighted; 6=terrible), and health status via EQ-5D-5L (0=worst health, 100=best health). A 10-point improvement in any OAB-q subscale score was considered clinically meaningful;[4] a 3-point improvement in total IPSS was considered clinically meaningful; a 0.5-point improvement was considered the minimal clinically important difference for IPSS-QoL.[5,6] This interim analysis included patients who completed ≥3 months of observation while receiving Vesomni (through Visit 3); 298 were evaluated for safety/tolerability; 251 were evaluated for QoL and treatment satisfaction.

Treatment with Vesomni yielded clinically meaningful improvements in OAB-q symptom bother score at Weeks 4–8 and 9–18, total and coping, concern, and sleep subscale scores at Weeks 4–8, and total and coping and sleep subscale scores at Weeks 9–18 (Figure 1). A clinically meaningful improvement in TS-VAS was also observed by Weeks 4–8 and was maintained through Weeks 9–18 (Figure 2). Health status via the EQ-5D-5L improved modestly from a mean of 65.2 at baseline to 72.1 at Weeks 4–8 and 69.8 at Weeks 9–18. Total IPSS score improved from 15.5 at baseline to 10.6 at Weeks 4–8 (mean of 4.7 points improvement) and to 10.9 at Weeks 9–18 (mean of 3.5 points improvement). IPSS-QoL scores improved by 1.2 points at Weeks 4–8 and by 0.9 points at Weeks 9–18; all improvements in IPSS scores were clinically meaningful. One hundred and fifty-one TEAEs were reported in 68 patients (22.8%); 131 (87.0%) were mild-to-moderate in severity. The most common TEAEs were constipation (6.0%), dry mouth (5.4%), and dyspepsia (3.0%); no deaths, serious adverse events, or cases of urinary retention requiring catheterisation were reported.

EUROPA is the first report of the treatment benefit and safety/tolerability of Vesomni in routine clinical practice; it demonstrated clinically meaningful improvements in health-related QoL and treatment satisfaction. These results support Vesomni as a treatment option for men with LUTS/BPH not adequately responding to monotherapy.

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INCIDENTAL PROSTATE CANCER (PT1A-PT1B) DETECTION AT BENIGN PROSTATIC HYPERPLASIA SURGERY IN THE MODERN ERA: ARE WE MODIFYING THE DETECTION RATE?

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Keywords: Incidental prostate cancer, benign prostatic hyperplasia (BPH), holmium laser enucleation of the prostate (HoLEP), transurethral resection of the prostate (TURP).

INTRODUCTION AND OBJECTIVES

Prior to the prostate-specific antigen (PSA) era, up to 27% of prostate cancers (PCas) were detected incidentally at the time of transurethral resection of the prostate (TURP).[1] In the last decades, the introduction of PSA in daily clinical practice decreased the rate of unexpected incidental PCa (iPCa) after benign prostatic hyperplasia (BPH) surgical treatment.[2,3] Moreover, the broad diffusion of novel diagnostic tools, such as multiparametric magnetic resonance imaging (MRI) has deeply changed clinical practice in the setting of PCa diagnosis.[4] For these reasons, we aimed to assess current rates and temporal trends of iPCa detection in the last decade.

METHODS

We collected data from 84 patients submitted to surgical treatment for BPH from January 2008–September 2016 at one tertiary-referral academic centre. All patients were comprehensively assessed with a detailed preoperative evaluation including age at surgery, BMI, digital rectal examination performed by a senior attending urologist and serum total prostate-specific antigen (PSA). Preoperative prostate volume was routinely assessed with transurethral prostate ultrasound (TRUS). A preoperative prostate biopsy was performed in case of suspected PCa, based on digital rectal examination, age, and total PSA. Patients with preoperative positive biopsy and/or PSA ≥10 ng/mL were excluded from the analysis. Histopathological specimens were available for all cases. Patients were categorised according to the year of surgery into three subsequent time-frames (i.e. 2008–2010 versus 2011–2013 versus 2014–2016). Descriptive statistics were applied to assess potential differences in overall clinical characteristics and rates of iPCa over time.

RESULTS

The three groups, 2008–2010 versus 2011–2013 versus 2014–2016, did not differ in terms of mean

standard deviation (SD) age (66 [SD: 8.1] versus 65.9 [SD: 7.2] versus 62.7 [SD: 6.6] years; p=0.5) mean total PSA (3.2 [SD: 2.3] versus 3.0 [SD: 2.3] versus 3.5 [SD: 2.4] ng/mL; p=0.1). Conversely, patients treated over the years 2014–2016 had significantly higher mean prostate volume (cc) (91.1 [SD: 3.8] versus 63.5 [SD: 6.5] versus 39.4 [SD: 1.9] mL; p=0.001) than over the previous two time slots. Overall, 380 (44.8%), 350 (41.3%), and 118 (13.9%) patients were treated with TURP, holmium laser enucleation of the prostate (HoLEP), and open prostatectomy (OP), respectively. A history of preoperative negative biopsy was more frequently reported during the period of 2008–2010 (121 [24.4%]) than in 2011–2013 (13 [10.8%]), and in 2014–2016 (7 [3%]) (p=0.00; chi^2: 5.4). Overall, iPCa was found in 46 (5.4%) patients, with 97.7% (45) of them having a Gleason Score 3+3 disease and 1 patient having a Gleason Score 4+4 disease. The rate of iPCA did not significantly differ among patients treated in 2008–2010 (28 [5.6%]) versus 2011–2013 (4 [3.3%]) versus 2014–2016 (14 [6%]; p=0.6). Similarly, rates of cT1a disease did not differ among groups: 23 (88.5%) versus 4 (100%) versus 13 (81.2%); p=0.5.

CONCLUSIONS

Despite the increase in PSA screening and the broad diffusion of innovative diagnostic tools for PCa detection, the rate of unexpected iPCa after BPH surgery did not significantly change in the last decade and ranges stably between 4% and 6%. Interestingly, a trend toward a decrease indication for preoperative prostate-biopsy was observed.

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CLINICAL PROFILE OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS WITH LOWER URINARY TRACT SYMPTOMS AND NEUROGENIC BLADDER. A CROSS-SECTIONAL STUDY

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Keywords: Neurogenic bladder, amyotrophic lateral sclerosis (ALS), lower urinary tract symptoms (LUTS).

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that typically involves upper and lower motor neurons. It is clinically characterised by a progressive weakening of the muscles that starts either in the bulbar region or

in the limbs and spreads, leading to death from respiratory failure in 3–5 years.

Lower urinary tract symptoms (LUTS) were previously thought to be infrequent features in ALS. When they occurred, they were largely attributed to reduced mobility since Onuf's nucleus remains relatively spared in the disease. However, we and others have shown that LUTS are reported by around 40% of ALS patients and that urinary incontinence (UI) is found in ≤30% of them.[1] Moreover, we have shown that these urinary symptoms are secondary to neurogenic bladder and therefore attributable to disease pathogenesis, although the underlying mechanisms remain unknown.

OBJECTIVES

Characterisation of LUTS among ALS phenotypes and their correlation with clinical characteristics may help us to understand the underlying pathophysiology. This could be important, since the different mechanisms leading to UI can have diverse impact on treatment and/or prognosis. This study aimed to describe differences in LUTS among the ALS phenotypes and their relationship with other clinical characteristics, including prognosis.

PATIENTS AND METHODS

Patients meeting criteria of classical ALS, progressive muscular atrophy (PMA), or primary lateral sclerosis (PLS) were recruited between May and November 2014 and followed-up until August 2016. Neurological and neuropsychological examinations were performed. Disability was assessed with the Revised ALS Functional Rating Scale (ALSFRS-R) score. Patients were categorised into bulbar or spinal according to the onset region. Muscle strength was measured using the Medical Research Council (MRC) rating scale. Executive and behavioural functions were also assessed.

Validated questionnaires of urinary symptoms (International Consultation on Incontinence Questionnaire - Short Form [ICIQ-SF], International Prostate Symptom Score [IPSS], and Overactive Bladder Awareness Tool [OAB-V8]) were self-administered. A complete pelvic and genital examination, dipstick test, prostate ultrasound, prostate-specific antigen levels (males), transabdominal ultrasonography, and urodynamic study were performed in clinically significant LUTS (csLUTS) patients who consented. Patients with csLUTS and abnormal urodynamic findings not related to pathology of the lower urinary tract were considered to have neurogenic bladder (NB).

Association between the different urinary symptoms scales, phenotype, and ALSFRS-R score was assessed using ordinal logistic regression models. Association of the clinical variables with presence of relevant urinary symptoms and NB was assessed using logistic regression models. We performed a multivariable survival analysis to study the effect of urinary symptoms in risk of death of the study population. We included, as covariates, other variables (age, bulbar onset, and phenotype) that affect survival in ALS patients. Death or tracheostomy were defined as endpoints.

RESULTS

Fifty-five ALS patients (37 classical ALS, 10 PMA, and 8 PLS) were included. Twenty-four patients reported csLUTS, and NB was demonstrated in 9 of them. LUTS were not influenced by age, phenotype, disability, cognitive or behavioural impairment, or disease progression, but female sex appeared to be a protective factor (odds ratio: 0.39, p=0.06). All NB patients were male and a subgroup, reporting LUTS early in the disease course, often showed other non-motor features and poor survival. Survival of csLUTS patients was similar to non-csLUTS (70.6 versus 62.9 months, p=0.69). More NB patients met the endpoint (death or tracheostomy) at last follow-up, and tracheostomy-free survival was shorter compared to patients without NB (70.6 versus 28.2 months respectively), although it was not statistically significant. We noticed that patients showing NB within 2 years from symptoms onset deteriorated rapidly and met the endpoint prematurely. In the multivariate survival analysis, age and urinary symptoms were the variables more strongly associated to survival, although statistical significance was not met (p=0.06 and p=0.08, respectively). See Figure 1 and Table 1.

CONCLUSION

LUTS are more frequent in male ALS patients but are not related to age or clinical characteristics. When reported early, LUTS could be a sign of rapid disease spread and poor prognosis. Further prospective longitudinal and neuroimaging studies are warranted to confirm this hypothesis.

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THULIUM VAPO-ENUCLEATION OF THE PROSTATE VERSUS HOLMIUM LASER ENUCLEATION OF THE PROSTATE FOR THE TREATMENT OF BENIGN PROSTATIC OBSTRUCTION: 6-MONTH SAFETY AND EFFICACY RESULTS OF A PROSPECTIVE RANDOMISED TRIAL

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Keywords: Thulium vapo-enucleation of the prostate (ThuVEP), holmium laser enucleation of the prostate (HoLEP), lasers, Ho:YAG, Tm:YAG; benign prostatic obstruction (BPO); benign prostatic hyperplasia (BPH), minimally invasive.

INTRODUCTION

Since the introduction of holmium laser enucleation of the prostate (HoLEP) into the armamentarium of benign prostatic hyperplasia (BPH) treatment, HoLEP has been proven to be a minimally invasive, size-independent method with excellent long-term results. Thulium vapo-enucleation of the prostate (ThuVEP), an alternative procedure mimicking the HoLEP technique, has been shown to be a size-independent procedure for the surgical treatment of BPH with low perioperative morbidity and good long-term results. However, no randomised controlled trial (RCT) has compared the ThuVEP technique with HoLEP in large volume BPH so far. We present the first RCT comparing the outcomes of ThuVEP with HoLEP in large volume BPH during 6-month follow-up.

METHODS

A RCT comparing ThuVEP with HoLEP was performed from February 2015–February 2016 at our department. A total of 94 consecutive patients were randomised to ThuVEP (n=48) or HoLEP (n=46). The patients were assessed preoperatively by means of International Prostate Symptom Score (IPSS), quality of life, maximum urinary flow rate (Qmax), post-void residual urine (PVR), prostate-specific antigen (PSA), and prostate volume measurement. The patients were reassessed using the same tests at 1-month and 6-month follow-up.

RESULTS

There were no statistically significant differences in any baseline characteristics between the groups. The median prostate volume was 80 mL. The median operative time was 60 minutes without

differences between the groups. There were no differences between the groups regarding the median catheter time (2 days) and postoperative stay (2 days). Clavien 1 (13.8%), Clavien 2 (3.2%), Clavien 3a (2.1%), and Clavien 3b (4.3%) complications occurred without differences between the groups. At 6-month follow-up, median Qmax (10.7 versus 25.9 mL/s), PVR (100 versus 6.5 mL), IPSS (20 versus 5), quality of life (4 versus 1), PSA (4.14 versus 0.71 µg/L), and prostate volume (80 versus 16 mL) had improved significantly ($p<0.001$) compared to baseline without differences between the groups. The median PSA decrease was 79.7%, which corresponded to a prostate volume reduction of 74.5% without differences between the groups. The reoperation rate was zero at 6-month follow-up.

CONCLUSIONS

ThuVEP and HoLEP are safe and effective procedures for the treatment of symptomatic large volume BPH. Both procedures give equivalent and satisfactory micturition improvement with low morbidity and sufficient prostate volume reduction at 6-month follow-up.

SUPRACOSTAL ACCESS FOR PERCUTANEOUS NEPHROLITHOTOMY IN MODIFIED SUPINE POSITION: FEASIBILITY, SAFETY, AND EFFICACY

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Keywords: Percutaneous renal surgery, percutaneous nephrolithotomy (PCNL), renal stone, ureteral stone, supracostal approach, subcostal approach.

Percutaneous nephrolithotomy (PCNL) has become the treatment of choice for large and staghorn renal calculi. The technique is classically performed in the prone position but the debate over which is the optimal patient position and the optimal puncture site is ongoing. The supine position has been found to be safe and effective,[1] but many studies have discouraged the supracostal approach because of the risk of intrathoracic complications. Therefore, we decided to assess the safety and feasibility of supracostal access for PCNL in the modified supine position. The position has been described in detail in a previous article.[2] Data from 96 patients with supracostal access (Group 1) were collected and compared to those from 100 patients with subcostal access (Group 2). Patient and stone characteristics were similar in both groups. The puncture was above the 12th rib in 76 patients (79.1%) and above the 11th rib in 20 cases (20.8%). Operative time and hospital stay was not significantly different between the two groups. There was also no significant difference in complications according to the Clavien–Dindo Classification between the two groups. There were no Grade-IVb or Grade-V complications. No instances of haemothorax, pneumothorax, nephropleural fistula, or renal artery pseudoaneurysm were noted. The stone free rate was 96.6% and 97.1% in Group 1 and Group 2, respectively ($p=0.13$).

The discussion after the presentation considered the advantages of the modified supine position. We stated that the main advantage was that when the colon fell, there was less risk of colon injury. Other advantages were shorter operative time because there was no need for a position change, reduction of radiation exposure, less cardiovascular and respiratory risks, passive evacuation of liquid, and small fragments due to the horizontal position of the Amplatz Sheath.

At the end of the session we concluded that supracostal PCNL is feasible, effective, and safe.

Supra PCNL should be attempted when indicated (e.g. staghorn and proximal ureteral calculi, calculi within a caliceal diverticulum). Nevertheless, the chairman of the session stated that the risk of lung or pleural injury increases above the 11th rib and this should be taken into consideration while performing supracostal access.

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A LIKERT ANALYSIS OF DOUBLE J STENT-RELATED URINARY SYMPTOMS ASSESSED BY THE URETERIC STENT SYMPTOM QUESTIONNAIRE AFTER SEMI-RIGID AND FLEXIBLE URETEROSCOPY

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Keywords: Lower urinary tract symptoms, stents, ureteroscopy, urinary calculi.

Many urologists still use double J ureteral stents at the end of semi-rigid and flexible ureteroscopy (ureteroscopic lithotripsy [URS] and retrograde intrarenal surgery [RIRS], respectively), although they are often unnecessary. As the worldwide spread of RIRS should be intended to increase efficacy but not morbidity, we decided to evaluate stent-related symptoms specifically after URS and RIRS using a specific validated questionnaire: the Ureteric Stent Symptom Questionnaire (USSQ).

The objective of our study was to assess double J ureteral stent-related urinary symptoms in detail after URS and RIRS with the USSQ, and to show this in an easily understandable way. We organised a prospective single-institutional observational study from January 2010–October 2015. After URS and RIRS with double J ureteral stent use, patients were asked to complete the validated Italian version of the USSQ. A descriptive statistical analysis and a Likert analysis were performed.

Two hundred and thirty-two patients completed and returned the USSQ, and 88% of patients stated that their urinary symptoms represented a problem, with 47% stating they represented either quite a bit of or a severe problem, and 79% noting they would feel mostly dissatisfied, unhappy, or terrible if they had to spend the rest of their life with their urinary symptoms. The Likert scale results showed in detail how stents are particularly associated with burning at voiding, urgency, a feeling of incomplete voiding, and macroscopic haematuria. Stratification by sex showed that urinary symptoms are more common and severe in females. Stratification by age showed that burning at voiding, a feeling of incomplete voiding and macroscopic haematuria are more common and severe in younger patients.

In conclusion, the use of double J ureteral stents after URS and RIRS is commonly associated with bothersome urinary symptoms and urinary symptoms represent a problem for the great majority of patients with females and younger patients being particularly affected. Therefore, stents should be used after URS and RIRS only when absolutely necessary and should be left in place for as little time as possible. See Figure 1 and Table 1.

REDO URETHROPLASTY AFTER UNSUCCESSFUL URETHRAL RECONSTRUCTION WITH BUCCAL MUCOSAL GRAFT

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OBJECTIVES

Substitution urethroplasty is the treatment of choice for patients with recurrent, extended urethral stricture, as the results of the still highly preferred endoscopic urethrotomy are very short lived. The challenge presented with this procedure is how to support and treat patients after an unsuccessful urethroplasty; the question is: what can we do and what should we offer such patients? Should it be a urethrostomy? Should it be regular urethral dilatation, or transurethral catheter as a last resort? Or should a redo urethroplasty be offered and would it be the better (but still risky!) option? We report the results of our prospective maintained database.

PROCESS

Between August 1994 and June 2015, 917 consecutive patients were prospectively evaluated after a single stage urethroplasty with buccal mucosal graft. Prior to this treatment, 112 of these patients (12.2%; 92 external, 20 own patients) had already undergone an unsuccessful urethroplasty previously (median age [range]: 51 [5–81]; stricture length [range]: 8 cm [1–23]; previous treatments [range]: 6 [2–22]). The redo urethroplasty was carried out exclusively as a ventral onlay.

Follow-up was carried out prospectively via standardised questionnaires detailing quality of life and urinary function (patient-reported). We recommended a residual urine sonography and uroflowmetry (3-monthly in the first year; 6-monthly for the following 4 years; yearly thereafter). In the case of a maximum flow rate of <15 mL/s and/or residual urine >50 mL, or in the case of urinary tract infection, a diagnostic urethrography and cystoscopy were performed.

RESULTS

Of the total participants, 92.8% (104/112) of patients could be evaluated. After a median of 54 months (range: 1–205), 9.6% (10/104) patients suffered a re-stricture. There was no difference in the two groups (away versus own patients).

CONCLUSIONS

A redo urethroplasty with buccal mucosal graft after an unsuccessful urethral reconstruction is associated with high success rates. The recurrence rate after the primary reconstruction of 8.2% (68/825) did not differ significantly as compared to the redo surgery in our centre.

IMPLICATIONS

As we return to the original problem and the questions asked at the start of this summary, we can draw the following implications. Firstly, the redo urethroplasty seems to be the most reasonable option for such patients, which if successful, could provide the best quality of life, as the micturition would still function naturally. Moreover, if unsuccessful, other options such as urethrostomy can still be performed. Secondly, the results, at least in our patients, are still good enough when compared with the primary repair. Thirdly, each patient should be counselled on an individual basis, with the pros and cons of every option stated and the patient should be informed about the slightly higher recurrence rate following the repeat surgery. The most important message taken from these results is that such cases, or better said, such high-risk cases, should only be operated on in high volume-experienced centres.

VALIDATION OF TUMOUR NECROSIS FACTOR ALPHA AS THE TOP UPSTREAM REGULATOR OF BLADDER REMODELLING DURING OUTLET OBSTRUCTION-INDUCED LOWER URINARY TRACT DYSFUNCTION

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Keywords: Bladder obstruction, microRNA (miRNA), genes, tumour necrosis factor alpha (TNF-α).

MicroRNAs (miRNAs) are small non-coding regulatory RNAs that are altered in patients with lower urinary tract dysfunctions (LUTD). miRNAs regulate gene expression and may cause molecular changes in the bladder wall during bladder outlet obstruction (BOO). Previously, using next-generation sequencing (NGS) of messenger RNAs and miRNAs in human patients' biopsies, we identified tumour necrosis factor alpha (TNF-α) as the top upstream regulator of signalling, potentially contributing to organ remodelling. Here we validated the NGS and pathway analysis in cell-based models using bladder smooth muscle (SM) cells and urothelial (UE) cells exposed to TNF-α.

TNF-α-responsive genes were selected based on LUTD patients' NGS data and *in silico* analysis. SM and UE cells were treated with 10 ng/mL TNF-α and RNA isolated. Regulation of TNF-α-induced genes was studied by quantitative real-time polymerase chain reaction (qRT-PCR) and NGS. nCounter® miRNA Expression Assays (NanoString, Washington, Seattle, USA) were used to profile miRNAs. A cell proliferation assay was performed to evaluate the proliferative effects of TNF-α. To determine whether NFκB signalling was affected by the altered miRNAs, NFkB-luciferase reporter assays were performed.

After TNF-α treatment, NFκB2, RelB, and TNFAIP3 showed a progressive time and concentration-dependent upregulation, and responses were stronger in SM cells compared to UE cells. TNF-α treatment increased cell proliferation. miRNA expression profiling identified 17 miRNAs altered in both SM and UE cells. miRNAs *miR-146a-5p, -21-5p, -1260a, -183-5p, -22-3p, -199a-3p, -199b-3p* were similarly regulated in patients and cell-based models. *miR-26b* was significantly induced in UE and SM cells, but downregulated in BOO. There was a cell-type-dependent difference in miRNA profiles, with SM cell-specific miRNAs downregulated after TNF-α treatment, in accordance with the downregulation of SMmarkers and loss of contractility in human patients. Transcriptome analysis of TNF-α treated cells was carried out and expression levels of predicted targets of disease-relevant miRNAs were identified. Ectopic over-expression of *miR-199a-5p* caused the downregulation of NFκB signalling in TNF-α-treated cells.

Our results confirm the important role of TNF-α in the regulation of BOO-specific miRNAs and identify miRNAs linking TNF-α signalling and fibrosis. Based on the reduced NFκB activation in *miR-199a-5p*-overexpressing SM cells and HEK293 cells, NFκB signalling may be directly affected by *hsa-miR-199a-5p,* which targets specific pathway elements. Compensatory upregulation of miRNAs inhibited by TNF-α might prevent organ remodelling and lead to novel therapeutic approaches for BOO-induced LUTD.

DETRUSOR BIOENGINEERING USING COMPRESSED COLLAGEN, ADIPOSE-DERIVED STEM CELLS, AND SMOOTH MUSCLE CELLS

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Keywords: Bladder, stem cells, tissue engineering.

INTRODUCTION

Conditions impairing bladder function in children and adults require an augmentation cystoplasty and other reconstructive procedures upon the failure of conservative therapy. Despite providing functional improvement, these procedures are associated with significant long-term complications such as bladder stone formation, recurring urinary tract infections, and malignancies, resulting in a strong clinical need for alternative therapies for these reconstructive procedures.[1-3]

Within the last years, various natural,[4,5] synthetic,[6] and hybrid[7] scaffolds for bladder engineering have been developed. However, improved bladder regeneration and the replacement of defective bladder tissue with functional equivalents have not been achieved yet and remain one of the major challenges in the field of bladder tissue engineering. Hence, the objective of this study is developing functional smooth muscle tissue for detrusor muscle replacement and improving the native detrusor muscle regeneration in a damaged bladder wall.

MATERIAL AND METHODS

Primary rat bladder smooth muscle cells (rSMCs) and adipose-derived stem cells (rADSCs) have been isolated and expanded, and rADSCs were differentiated into rSMC-like cells (pADSCs) using an established protocol. After flow cytometric characterisation, the rSMCs and pADSCs were mixed in ratios of 1:1, 1:2, and 1:3 (rSMCs:rADSCs) and grown for ≤3 weeks in culture. In addition to the two-dimensional (2D) co-culture, compressed collagen (CC) hydrogel scaffolds containing these cell compositions were fabricated. Cells grown in the 2D and three-dimensional (3D) microenvironments were evaluated and compared concerning their morphology, SMC-marker expression, viability, proliferation, and functionality (contractility). Furthermore, the effect of direct, cell-to-cell co-culture, and indirect co-culture using Transwell® (Sigma-Aldrich, St. Louis, Missouri, USA) inserts was assessed by viability test and in/on-cell western blot analyses.

RESULTS

After defining the optimal cell culture conditions the co-cultures showed high viability and proliferative capacity in the CC scaffolds, which led to the development of interconnected cell layers and microtissue formation in the hydrogel after 1 week. A significantly increased cellular proliferation was observed in all directly co-cultured specimens compared to the monocultures. Indirect co-culture led to an increased pADSC-survival and a cell ratio-dependent improvement of rSMC-proliferation. The overall pADSC-proliferation was also increased, yet unaffected by the cell ratio. Over 8 days of growth the 1:1 ratio exhibited the steadiest proliferation compared with the 1:2 and 1:3 ratios. A strong expression of the rSMC-specific markers α-smooth muscle actin, calponin, MyH11, and smoothelin was detected after 1 week, becoming rather pronounced after 2 weeks. The expression of all rSMC-specific markers over all cell ratios reached nearly the native rSMC-marker expression after 2 weeks of co-culture and the contractility did not reach significance among each other and compared to the rSMC monoculture after 48 hours. See Figure 1.

CONCLUSION

In summary, our results showed an improved cell proliferation and survival of SMC-pADSC co-cultures compared to mono-cultures of each cell type in 2D cell culture experiments. Further 3D-CC experiments confirmed that in fact a co-culture of these cell types proves beneficial for the formation of smooth muscle tissue. Thus, the combination of rSMCs and pADSCs with CC may help to engineer functional detrusor muscle tissue by overcoming current limits of tissue engineering, namely poor primary cell survival, proliferation, phenotype instability, and tissue function.

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VALIDATION OF AUTOMATED KIDNEY STONE VOLUMETRY IN LOW DOSE COMPUTED TOMOGRAPHY

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Keywords: Urolithiasis, stone volumetry, percutaneous nephrolithotomy (PNL).

INTRODUCTION AND OBJECTIVES

In the clinical trials on urolithiasis, stone size is mostly assessed by maximum diameter; however, most stones are not spherical. This could possibly result in bias and misleading results, because stone fragmentation time, the number of fragments, extraction time, and other outcomes are dependent on stone size. The current use of the diameter stands for an implicit correlation between the real stone volume and the diameter.

Software solutions can provide an automated assessment of a stone's volume by clicking on the stone of interest on a computed tomography (CT) scan. We validated this software (syngo.via/ Siemens, Forchheim, Germany) at our institution and evaluated the variation between diameter, expected volume, and volumetry results.

MATERIAL AND METHODS

Over 100 stones were measured by three urologists independently, who assessed the maximum diameter using a digital sliding caliper and the volume using a

water displacement/overflow method. The interrater correlation was calculated and the mean values were used as a reference. The same stones were then positioned in a radiologic phantom and CT scans were acquired at low-dose settings. Three radiologists measured the maximum diameter and volume using the software for automated measurement with 0.75 mm reconstructions.

In order to assess the value of the automated stone volumetry, we calculated the expected volume using the radiological maximum diameter and the formula: $V=4/3\ \pi r^3$ and compared the calculated volume to the volume measured with volumetry.

RESULTS

The interrater correlation for the reference measures was very good, qualifying those measurements as reference values. Some stones with the same diameter differed in volume by a factor of 2. There was a close correlation of the reference volume with the automated radiologic volume assessment, meaning that the displayed values are reliable and useful for size evaluation. The correlation of the expected volume with the reference volume was significantly worse.

CONCLUSION

Automated measurements of stone volume based on CT scans is possible and the accuracy is significantly higher compared with volumetric calculations based on the diameter.

The currently used size parameter 'max diameter' causes potential bias in studies. In order to avoid misleading results in clinical trials, size should be measured as volume or a combination of diameter and volume. Therefore, easy-to-use software solutions must be developed and introduced into clinical/scientific practice.

FIVE-YEAR PROSPECTIVE STUDY EVALUATING HEALTHCARE-ASSOCIATED INFECTIONS IN A UROLOGY WARD: RISK FACTORS, MICROBIOLOGICAL CHARACTERISTICS, AND RESISTANCE PATTERNS

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Keywords: Extended-spectrum betalactamase (ESBL) producing bacteria, healthcare-associated infections (HAIs), micro-organisms, risk factors, urology.

INTRODUCTION

Healthcare-associated infections (HAIs) in urological patients have special characteristics due to specific risk factors such as a high prevalence of urinary catheterisation and as surgery is commonly performed during hospitalisation.[1-3] Furthermore, an adequate knowledge of the microbiological patterns is of paramount importance to optimise the outcomes.[4,5] Our purpose was to review the incidence and characteristics of HAIs in patients admitted in a urology department.

MATERIAL AND METHODS

We carried out a prospective observational study over 5 years (November 2011–September 2016) evaluating the incidence, types of HAIs, risk factors, microbiological characteristics, and patterns of susceptibility to antibiotics among patients admitted to our urology ward.

RESULTS

Out of 8,138 patients, 518 (6.4%) experienced some type of HAI. The evolution in the incidence of HAIs over the time is shown in Figure 1. The most common types were urinary infections (70.4%) followed by surgical site infections (21.7%). Factors associated with a higher risk of HAIs were older age (odds ratio [OR]: 1.009; p=0.002), male sex (OR: 1.225; p=0.017), arterial hypertension (OR: 1.213; p=0.033), heart disease (OR: 1.244; p=0.043), liver disease (OR: 1.492; p=0.035), prior urinary infection (OR: 3.402; p<0.001), immunosuppression (OR: 2.058; p<0.001), American Society of Anaesthesiologists (ASA) Score III-IV (OR: 1.298; p<0.001), and an indwelling urinary catheter prior to admission [OR: 1.987; p<0.001] or during hospitalisation (OR: 1.379; p<0.001). Multivariate analysis confirmed several risk factors: immunosuppression (OR: 1.735; 95% confidence interval [CI]: 1.138–2.646; p=0.010), ASA Score III-IV (OR: 1.217; 95% CI: 1.063-1.392; p=0.004), prior urinary infection (OR: 2.648; 95% CI: 1.161–6.041; p=0.021), and an indwelling urinary catheter prior to admission (OR: 1.838; 95% CI: 1.427–2.366; p<0.001). Surgical procedures associated with the highest incidence of HAIs were open prostatic surgery (7.2%), renal surgery (7.2%), and radical cystectomy (51.6%).

The most commonly isolated pathogens were *Escherichia coli* (25.6%), followed by species of *Enterococcus* (18.2%), *Klebsiella* (13.8%), and *Pseudomonas* (11.7%). *Staphylococcus aureus* and *Candida* were isolated in 6.1% and 5.1% of positive cultures, respectively (Figure 2). No micro-organisms were isolated in 28.4% of patients. *E. coli* showed resistance rates of 50% for fluoroquinolones, 10.9% for amikacin, and 1.9% for carbapenems. *Klebsiella* spp. showed resistance rates of 44.8% for third-generation cephalosporins, 39.7% for fluoroquinolones, and 6.8% for carbapenems. Among cultures where *E. coli* was isolated, 26.9% were extended-spectrum betalactamase (ESBL)-producing bacteria; this figure was 42.4% when *Klebsiella* was isolated. *Enterococcus* was the most commonly isolated micro-organism after cystectomy and showed resistance rates of 50.7% for fluoroquinolones and 1.3% for vancomycin. *Pseudomonas aeruginosa* showed resistance rates of 52% for quinolones, 34% for carbapenems, and 22% for amikacin.

Among patients with prior urinary infections, the incidence of HAIs was 18.5% and the most commonly isolated micro-organism was *Klebsiella*, which represented 28.2% of positive cultures and 72.7% were ESBL-producing *Klebsiella*. Among those with immunosuppression, the incidence of HAIs was 11.8%, and the most commonly isolated micro-organisms were *Klebsiella* (31.6%), *E. coli* (21.1%), and *Enterococcus* (18.4%).

DISCUSSION

Observational studies reviewing HAIs are required in order to decrease the incidence and to optimise the management of infections.[4,6,7] Our series showed that being aware of HAIs may reduce HAIs from 7.0% to 5.5%. Furthermore, observational studies permit the determination of risk factors for infections and microbiological patterns in each patient and therefore enable the empirical antibiotic treatment to be tailored according to the characteristics of the patient.[8-10]

In conclusion, the risk factors related to HAIs were comorbidities, prior urinary infection, and a urinary catheter before admission. Although *E. coli* was the most frequently isolated micro-organism, *Enterococcus*, *Klebsiella*, and *P. aeruginosa* were commonly found. ESBL-producing *Enterobacteriaceae* occurred in 26.9% of cultures with *E. coli* and 42.4% of cultures with *Klebsiella*.

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CHARACTERISATION AND PERSONALISED TREATMENT RESPONSE IN PRIMARY AND METASTATIC PROSTATE CANCEROIDS

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Keywords: Prostate cancer (PCa), cancer stem cells, organoids, patient derived xenografts, androgen inhibitors.

Prostate cancer (PCa) associated mortality results from metastasis to bone and resistance to androgen deprivation or cytotoxic therapy. Despite early detection of primary PCa, advanced castration resistant PCa and bone metastases are detected in 10% of patients at the time of initial diagnosis. The majority of recurrences may be due to cancer cells with stem cell-like properties (CSC-like). These could be therapy-resistant in a dormant state at the primary site or have metastasised prior to diagnosis of the primary tumour. CSC-like cells are the most tumourigenic and metastatic; however, current treatments target the differentiated tumour bulk cells. Understanding the mechanisms of PCa tumour initiation and metastasis by CSC-like cells is crucial for proper prognosis of high-risk patient groups. We aimed to determine whether CSC-like cells from metastatic tissues are responsive to the standard compounds used for the treatment of the primary tumour type.

To model metastatic CSC-like cells we generated organoids from patient-derived tissues (here termed 'canceroids') and established patient-derived xenografts. Organoid culture protocols are based on previously published experimental approaches for murine[1,2] and human prostate organoids.[2,3] Response to androgens (dihydrotestosterone), cytotoxic compounds (e.g. cabazitaxel and docetaxel),

and androgen modulating agents (e.g. abiraterone and enzalutamide), are being tested on the canceroids using viability (CellTiter Glo®, Promega Corporation, Madison, Wisconsin, USA) assays and three-dimensional (3D) imaging by confocal and light sheet microscopy.

Canceroids maintain key features of the CSC-like cells, previously characterised on the tumour itself. In particular, the known luminal phenotype of BM18 is evidently maintained in the BM18 canceroids, based on positive cytokeratin (CK)18 and absent CK5 expression. LAPC4 canceroids contain CK5 and CK18 cells, in line with the mixed basal and luminal phenotype. Imaging of PSA and cytokeratin distribution confirms the luminal phenotype of the canceroids. BM18 and LAPC9 canceroids are maintained both in the presence and absence of dihydrotestosterone, indicating that androgen independent growth properties of the tumour are conserved in the canceroids. Imaging-based viability assays (Hoechst live-cell dye) indicate that LAPC9 canceroids respond to the chemotherapeutics cabacitaxel and docetaxel and the hormone inhibitors abiraterone and enzalutamide.

Identification of the oncogenic properties of metastatic CSC-like subpopulations has both prognostic and therapeutic applications. The establishment of CSC-derived organoids from bone metastatic tissue is the first step towards routine derivation from metastatic or primary PCa tissues as a potential platform for personalised drug compound evaluation.

The points of discussion when this abstract was presented at the European Association of Urology (EAU) Congress 2017 were the time-related advantages of canceroid generation for drug screens purposes versus patient-derived xenograft models and the future potential of diagnostic tests using patient-derived canceroids. Furthermore, the incorporation of stromal and immune cells in canceroid cultures was discussed.

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NOVEL CHRONIC TIBIAL NEUROMODULATION TREATMENT OPTION FOR OVERACTIVE BLADDER SIGNIFICANTLY IMPROVES URGENCY/URGE URINARY INCONTINENCE AND NORMALISES SLEEP PATTERNS: INITIAL RESULTS

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Keywords: Percutaneous tibial nerve stimulation, chronic tibial nerve modulation, idiopathic overactive bladder, neurogenic overactive bladder, onabotulinumtoxin A, sacral nerve modulation, quality of life.

According to the European Association of Urology (EAU), 20–≥30% of adults experience urinary incontinence, while up to an estimated 30% of females aged 30–60 years experience urinary incontinence.[1] Those patients who are identified as having an overactive bladder (OAB) suffer urgency or even urinary urgency incontinence, which are initially treated with medication. In spite of improved drug delivery systems and pharmacological advancements, this treatment remains refractory to medical treatments.

At the next level the EAU guidelines suggest onabotulinumtoxin A, sacral nerve modulation, or percutaneous tibial nerve stimulation;[1] however, the limited lasting effect of onabotulinumtoxin A[2] requires that patients need repeated injections into the detrusor muscle. Similarly, patients see disadvantages with sacral nerve modulation because of the surgery required to implant the electrodes into the gluteal and battery maintenance issues. Furthermore, implants limit the ability to do diagnostics, such as magnetic resonance imaging (MRI).[3] In recent years, percutaneous tibial nerve stimulation has become available, but the stimulation had to be performed in the office once a week for 20 minutes.[4,5]

With a chronic implant (Figure 1) and an external device (Figure 2), the patient can become more independent, without almost any diagnostic restrictions. The tibial nerve stimulation via the sacral plexus is known to control bladder function, but the actual mechanism of action has still not yet been identified.[6] We report our preliminary experience with a minimally invasive, implantable wireless neuromodulation system to perform chronic tibial nerve modulation.[7]

The primary inclusion criteria was adult patients with refractory OAB without obstructive/infective lower urinary tract and not taking any anti-muscarinic and beta-3 adrenergic agonists. From two centres, 21 patients were enrolled and 4 were excluded. After informed consent, the electrode was implanted in the leg along the tibial nerve 4–7 cm above the medial malleolus through a 5 mm skin incision in local anesthesia. The wireless Nautilus antenna assembly was the program used to control the stimulation parameters. Patients were asked to activate the implant on a subsensory threshold during the evening or while sleeping (8 hours).

All enrolled patients tolerated the procedure well. At the end of the 60–90-day follow-up, 5 patients had lead migration, 2 required revision, and other implants were removed. In 1 patient, the implant seemed not to cause any effect, independent of the amplitude.

During the early follow-up period, significant improvement in Incontinence Quality of Life (I-QOL) and Overactive Bladder Questionnaire (OABq) scores were observed ($p<0.05$). In addition, urgency incontinence episodes, Global Response Self-Assessment (GRS), and Patient Perception of Intensity of Urgency Scale (PPIUS) demonstrated a significant improvement. Although the mean number of voids remained unchanged, the mean voided volume increased by 70 mL. Those who suffered from nocturia normalisation reduced to an average of <1 incident per night. By the end of the 90-day evaluation, I-QoL and OABq scores reflected a delayed but significant improvement.

This initial pilot study demonstrates that chronic tibial nerve modulation is safe and effective with encouraging results. Surgical and implant modifications have been made to ensure that the chronic implant remains in its optimal position. US Food and Drug Administration (FDA) studies have been initiated due to these encouraging results and plans are underway to verify the findings on a larger scale.

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PREVENTING URETHRAL TRAUMA FROM INADVERTENT INFLATION OF CATHETER BALLOON IN THE URETHRA DURING CATHETERISATION: EVALUATION OF A NOVEL SAFETY SYRINGE AFTER CORRELATING TRAUMA WITH URETHRAL DISTENSION AND CATHETER BALLOON PRESSURE

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Keywords: Urethral trauma, urethral catheterisation, urethral rupture, urethral injury, urethral catheter, safety device, safety syringe.

Urethral catheterisation is a routine task that is frequently performed within a healthcare setting. Almost 25% of hospitalised patients are catheterised during their inpatient stay.[1] Urethral injury typically occurs in men when the catheter's anchoring balloon is inadvertently inflated inside the urethra.[2] Short-term complications include pain, bleeding, and acute urinary retention.[2] Urethral rupture can lead to the long-term complication of urethral stricture disease and may require urethral reconstruction in severe cases.[2]

There are currently no studies that demonstrate urethral strain thresholds for rupture during traumatic urethral catheterisation. Our aim was to investigate internal urethral diametric strain and threshold maximum inflation pressure as parameters for urethral rupture during inadvertent inflation of a catheter anchoring balloon in the urethra. In addition, we also designed and evaluated a novel safety device with the inability to cause urethral trauma, despite inadvertent balloon inflation in the urethra based on these parameters.

Inflation of a urethral catheter anchoring balloon was performed in the bulbar urethra of 21 *ex vivo* porcine models using 16 Fr catheters. Urethral trauma was characterised and graded with retrograde urethrography. Urethral rupture was correlated with internal urethral diametric strain (%) and maximal urethral pressure threshold values in kilopascals (kPa). Internal urethral diametric strain was calculated by averaging urethra luminal diameter proximal and distal to the traumatised site, and maximum luminal diameter at the traumatised site. Urethral catheters were then inflated in the bulbar urethras of seven fresh male cadavers using a standard syringe and a prototype safety-syringe (Figure 1). The plunger of the standard syringe was depressed until opposing resistance pressure generated by the urethra prevented further inflation of the anchoring balloon. The plunger of the prototype safety-syringe was depressed until sterile water in the syringe decanted through an activated safety threshold pressure valve (Figure 1).

Retrograde urethrography demonstrated that porcine urethral rupture consistently occurred at an internal urethral diametric strain >40% and a maximum inflation pressure >150 kPa (Figure 2). The mean±standard deviation maximum human urethral threshold inflation pressure required to activate the safety prototype syringe pressure valve was 153±3 kPa. In comparison, the mean maximum inflation pressure was significantly greater using the standard syringe than the activated prototype syringe (452±188 kPa, [p<0.001]).

Internal urethral diametric strain and threshold maximum inflation pressures are important parameters for designing a safer urethral catheter system with lower intrinsic threshold inflation pressures. We have validated our porcine and cadaver findings in human male-to-female transgender urethral models and have recently implemented our safety device into clinical practice in Tallaght Hospital, Dublin, Ireland for patients requiring urethral catheterisation. This transition of a safety device from bench to bedside was commended during my presentation during March 2017, held at the European Association of Urology (EAU) congress, hosted in London, UK.

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PSYCHOLOGICAL DISTRESS IN PATIENTS UNDERGOING SURGERY FOR UROLOGICAL CANCER: A SINGLE-CENTRE CROSS-SECTIONAL STUDY

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Keywords: Prostate cancer, kidney cancer, bladder cancer, anxiety, depressive disorder, psychological distress.

There has been increasing interest in the literature on the disease-specific psychological wellbeing of patients with cancer, and it has been estimated that less than half of all cancer subjects are properly identified and subsequently treated for anxiety or depression.[1] It is now widely recognised that psychosocial care is a crucial part of high-quality cancer care centres.[1] An elevated level of anxiety increases the risk associated with surgery (such as elevated heart rate, blood pressure, or the need for more medication to maintain an adequate level of sedation during procedure), including the morbidity and mortality.[2] Unfortunately, significant psychological disorders usually remain undetected and underestimated until their impact on quality of life becomes more visible.[3] This underestimation highlights the need to investigate different indicators of the psychosocial risk in oncology populations.[4]

The aim of the present study was to assess the prevalence of preoperative anxiety, depression, and psychological distress using validated self-administered questionnaires in patients with urological malignancies (prostate, bladder, and

renal) undergoing radical surgery. We performed a cross-sectional study in consecutively enrolled patients with bladder, kidney, or prostate cancer, scheduled for surgery. Demographic data, socioeconomic status, education level, and diagnoses were recorded. Patients with a previous diagnosis of depression or anxiety were excluded.

We evaluated the level of clinically meaningful depression and anxiety with two assessment tools: The Hospital Anxiety and Depression Scale ([HADS]; a score ≥8 indicated the presence of anxiety and depression; a score ≥11 indicated clinical anxiety and depression) and the State-Trait Anxiety Inventory (STAI). In order to determine variables related to depression and anxiety among the demographic variables, logistic regression analyses were conducted with $p<0.05$ considered as statistically significant. Two hundred and twenty consecutive patients admitted for oncological disease had their psychological profile evaluated.

Two hundred and seven patients completed the questionnaires and were included in the final study. The patients presented a mean age of 70.8 (±10.8) years, 89% were male (n=184), and 19% of patients presented previous cancer. Patients more frequently underwent surgery for bladder tumours (60.4%) and the most common type of surgery was transurethral resection. The most frequent procedures were performed for bladder tumours (60.4%), with transurethral resection the most common type of surgery (52.7%) followed by radical prostatectomy (24.6%). The mean STAI-state score was 19.3 (±10.3), and the mean STAI-trait score was 18.4 (±11.9) points. Patients showed HADs depression and anxiety scores of 3.3 (±3) and 5.6 (±3.3) points, respectively. Female patients showed a higher level of anxiety and STAI-trait compared to males. See Table 1.

The present results showed that our patients had lower levels of anxiety and depression than those described in the literature. Sex, tumour type, and surgical approach were significantly related to psychological distress in patients undergoing surgery for urological cancer. Females and patients with a kidney tumour and patients undergoing radical nephrectomy presented higher levels of anxiety. Patients with radical cystectomy showed a higher level of STAI-state compared with other surgeries.

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EDITOR'S PICK

Although a rare condition, presence of an adrenal cortical carcinoma should be suspected in adrenal masses, particularly in those >5 cm in size. Radiology, including magnetic resonance imaging (MRI) or computerised tomography (CT) of the abdomen, may be suggested if there is a possibility that it is a malignant mass due to the presence of possible invasive findings. Surgery is an important part of management, and especially in larger cases, open surgery may be more feasible and safe.

Dr Abdullah Erdem Canda

ADRENAL CORTICAL CARCINOMA: CLINICAL PERSPECTIVES

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ABSTRACT

Adrenal cortical carcinoma (ACC) is a rare malignant tumour which arises from the adrenal cortex with diverse clinical manifestations due to excessive hormone production, with Cushing's syndrome and virilisation being the most common features. The diagnosis of ACC relies on clinical, hormonal, and imaging features before surgery and pathological examination after tumour removal. Pathological assessment of Weiss score and the Ki-67 labelling index play an important role in diagnosis and prognosis. The tumour, lymph node, and metastasis (TNM) classification, established by the European Network for the Study of Adrenal Tumors (ENSAT) is used for staging. Currently, complete surgical resection is the only treatment option for ACC that has a curative intent, with no reported difference in overall recurrence or mortality between open and laparoscopic adrenalectomy. Mitotane is used as an adjuvant therapy after surgery for high-risk patients and as primary treatment for unresectable and advanced cases; however, it has a narrow therapeutic index and regular blood monitoring is essential. The role of chemotherapy and radiotherapy in ACC is unclear with limited studies and varying results. To date, trials which have been conducted for novel agents revealed disappointing results. Currently, trials are underway for agents targeting steroidogenic factor-1, mechanistic target of rapamycin (mTOR), and Wnt signalling pathways, as well as inhibitors of acetyl-coA cholesterol acetyltransferase 1. Unfortunately, ACC has an aggressive natural course with high recurrence rate, and a reported 10-year survival of 7% after treatment.

Keywords: Adrenocortical carcinoma, adrenal tumours, Weiss score, Ki-67 labelling index, mitotane.

INTRODUCTION

Adrenal cortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with a reported annual incidence of approximately 1–2 cases per million.[1,2] In the USA, the incidence is 0.7 cases per million per year and ACC accounts for 0.2% of all cancer deaths.[3,4] It can occur at any age although there are two peak incidences: in early childhood and the 4th–5th decades of life. Women are more frequently affected with a female to male ratio of 1.5–2.5:1.[4]

GENETIC PREDISPOSITION

Inherited

The current understanding of the pathogenesis of ACC is incomplete and limited. Although most cases of adult ACC are sporadic, paediatric ACC can be associated with several genetic disorders, such as Li–Fraumeni syndrome (LFS), Beckwith–Wiedemann syndrome, multiple endocrine neoplasia Type 1, Carney complex, congenital adrenal hyperplasia, McCune–Albright syndrome, and familial adenomatous polyposis. Thus, *TP53* mutations, seen in LFS and the alterations of the insulin-like growth factor 2 (IGF-2) of Beckwith–Wiedemann syndrome, are considered to be involved in the pathogenesis of ACC. Underlying LFS is diagnosed in 50–80% of all children with ACC, whereas it accounts for only 3.9–5.8% of adult onset ACC. In a recent study of 114 patients with ACC, 3.2% were reported to have Lynch syndrome, and germline mutations of *MLH1* and *MSH6* were identified in addition to *MSH2* mutations detected in previous case reports of ACC with Lynch syndrome.[5]

Acquired

Genomic studies, such as exome sequencing, have confirmed that inactivating mutations of *TP53* and activating mutations of the proto-oncogene b-catenin (*CTNNB1*) are implicated in the tumourigenesis of ACC.[6,7] A gene involved in the Wnt signalling pathway, *ZNRF3* (Zinc and ring finger protein 3), is reported to be the most frequently altered in ACC.[7] In addition, comparative genomic hybridisation detects chromosomal gains at 5, 7, 12, 16, 19, and 20 as well as losses at 13 and 22. A specific CpG island methylator phenotype is found in association with hypermethylation of the promoters of specific genes, such as *H19, PLAGL1, G0S2*, and *NDRG2*. Moreover, some studies identified a significant upregulation of *miR-483* and a downregulation of *miR-195* and *miR-335* in ACC.[8]

Recently, a new international collaboration as part of The Cancer Genome Atlas (TCGA) has identified several new genes that are associated with ACC, based on samples of 91 cases from countries across four continents; these genes are *PRKAR1A, RPL22, TERF2, CCNE1*, and *NF1*. Amplification of *TERF2* and telomerase was found in several samples, suggesting that telomere maintenance could be involved in the development of ACC.[9] In this recent study, 16% of the samples had a homozygous deletion of *ZNRF3* with 19.3% having some alteration in this gene, which is in accordance with previous findings.[7,9] Profound genomic instability, such as whole-genome doubling, is associated with an aggressive clinical course in ACC.[9]

Though IGF-2 is overexpressed in most cases of ACC, IGF-1 receptor-mediated downstream activation of the protein kinase B Akt/mechanistic target of rapamycin (mTOR) pathway does not play a major role in carcinogenesis. Studies using inhibitors of IGF-1R/mTOR signalling pathway revealed minimal tumour responses. Expression of hepatocyte growth factor (HGF) and its receptor, cMET, is increased in ACC, and HGF/cMET activation is associated with increased cell proliferation, reduced apoptosis, tumour-related angiogenesis, chemotherapy resistance, and cell survival.[10]

Table 1: Weiss scoring system.

Histological criteria	Score 0	Score 1
Nuclear grade*	1 and 2	3 and 4
Mitoses	≤5 for 50 fields ×400	≤6 for 50 fields ×400
Atypical mitoses	No	Yes
Clear cells	>25%	≤25%
Diffuse architecture	≤33% surface	>33% surface
Confluent necrosis	No	Yes
Venous invasion	No	Yes
Sinusoidal invasion	No	Yes
Capsular infiltration	No	Yes

*Grade 1: (round nuclei, homogenous, small size, no nucleoli); Grade 2: (nuclei slightly irregular, more voluminous, conspicuous nucleoli at ×400); Grade 3: (irregular nuclei, voluminous nucleoli at ×100); Grade 4: (the same as Grade 3 with monstrous cells and very irregular nuclei).

CLINICAL PRESENTATION

Clinical presentation of ACC is heterogeneous and the natural history can be highly variable. Many ACCs are asymptomatic and non-functional as adrenal incidentalomas identified on abdominal imaging; however, approximately 60–70% of ACCs in adults present with clinical syndrome of autonomous adrenocortical steroid excess, mainly Cushing's syndrome or worsening androgenisation in females.[11] Hormonally inactive ACCs present with symptoms related to local mass effects of the tumour, such as abdominal discomfort, back pain, nausea, or vomiting. Due to their deep location in the retroperitoneum, the majority of ACCs are large and locally advanced at the time of diagnosis. Frequently, ACCs invade adjacent large vessels, such as the renal vein or inferior vena cava.[12]

The majority of ACCs secrete a variable combination of glucocorticoids, mineralocorticoids, and sexual steroids. While clinical Cushing's syndrome and virilisation in females are the most common manifestations of hormonally active ACCs, they can also present with features of hyperaldosteronism, such as hypertension and profound hypokalaemia, or pheochromocytoma. Oestrogen hypersecretion is rare with gynaecomastia and testicular atrophy present in only 5–10% of male patients who are pathognomonic for ACC.[13] Children tend to have more functioning ACCs than adults. Virilising tumours are more prevalent in children because ACCs originate from the persistent fetal zone of the adrenal cortex, which produces dehydroepiandrosterone sulfate (DHEA-S).[14]

DIAGNOSIS

Imaging

Various imaging techniques, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have greatly increased the detection rates of adrenal masses. However, no single imaging method can identify an adrenal mass as ACC. Some radiological features that suggest the likelihood of ACC include large tumour size, irregular margin, lobulated shape, heterogeneous appearance (due to haemorrhages and/or necrotic areas), calcifications, low fat content, and high attenuation on an unenhanced CT with irregular enhancement after contrast.[7,15,16] ACC is more likely if the mass is >4 cm (sensitivity 97%; specificity 52%) and >6 cm (sensitivity 91%; specificity 80%).[17]

Table 2: Tumour, lymph node, and metastasis staging system for adrenal cortical carcinoma.

Stage	Characteristics
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0 T3–T4, N0–N1, M0
IV	Any T, any N, M1

T1: tumour ≤5 cm; T2: tumour >5 cm; T3: tumour infiltration into surrounding tissue; T4: tumour invasion into adjacent organs or venous tumour thrombus in vena cava or renal vein; N0: no positive lymph nodes; N1 positive lymph node(s); M0: no distant metastases; M1: presence of distant metastasis.

Low fat concentration of malignant lesions produce high attenuation on unenhanced CT; hence, it is recommended to perform a preliminary unenhanced CT attenuation measurement followed by an intravenous contrast scan for optimal imaging of the adrenal glands.[13] A cut-off value of <10 HU in unenhanced CT has been used for the diagnosis of benign lesions. However, a recent analysis from the German ACC registry suggests 13 HU is the most sensitive threshold to distinguish adenoma from carcinoma.[18] If unenhanced CT is indeterminate, a contrast enhanced CT should be performed to detect the washout, which is either absolute (the pre-contrast density is known) or relative (only a portal venous phase baseline is available), where an absolute washout of >50% suggests a benign lesion.[7,13]

Overall, MRI is as accurate as CT in differentiating adrenal adenomas and carcinomas, with a reported sensitivity of 84–100% and a specificity of 92–100%, similar to unenhanced CT.[13] The presence of isointense to hypointense signals on T1-weighted images, a hyperintense signal on T2-weighted images and a heterogeneous signal drop on chemical shift are the MRI features helpful in the diagnosis of ACC, where CT fails to characterise the adrenal lesion perfectly.[19,20]

In addition, imaging plays an important role in staging as well as assessing the involvement of surrounding organs and vessels to evaluate the feasibility of radical surgery, and to monitor treatment response during follow-up. MRI is

preferred for assessment of vascular invasion, whereas enhanced CT is extremely useful to detect organ invasion and metastatic spread. Three-dimensional reconstruction technology of CT or MRI images provide more detailed information about morphology and the anatomical relationship of ACCs, thus helping clinicians to develop an accurate surgical strategy, particularly for performing endoscopic or laparoscopic surgery.[21]

^{18}F-fluorodeoxyglucose positron emission tomography (PET) is a second-line investigation for indeterminate cases or in staging of known ACC. In patients with impaired renal function, PET/CT may be an alternative to CT. PET was reported to be more sensitive than CT in the detection of local recurrence, while CT was more sensitive in detecting small peritoneal or lung metastases.[22] PET/CT also demonstrates response to chemotherapy earlier than CT, as well as predicting the chemotherapeutic response of ACC before anatomic changes are detected with CT. Moreover, PET/CT may be useful for selecting the optimal treatment in patients with advanced disease.[23]

Advanced imaging modalities, such as ^{11}C-metomidate PET and ^{123}I-iodometomidate single-photon emission computed tomography (SPECT), use metomidate which binds to *CYP11B* enzymes expressed in the adrenal cortex and are taken up by adrenocortical tissue. Such techniques were recently demonstrated to be useful in differentiating ACC from metastatic carcinoma.[24]

Hormonal Assessment

As ACCs secrete excessive adrenal hormones, the European Network for the Study of Adrenal Tumors (ENSAT) recommends a detailed pre-operative endocrine assessment for suspected ACC including basal cortisol, adrenocorticotropic hormone, dexamethasone suppression test, urinary free cortisol, DHEA-S, 17-hydroxyprogesterone, testosterone, androstenedione, and oestradiol. Measurements of plasma free metanephrines or urinary fractionated metanephrines and the aldosterone/renin ratio is also recommended to exclude pheochromocytoma and primary hyperaldosteronism, respectively.[25]

Pathology

Macroscopically, most ACCs are large, heterogeneous tumours with necrosis and invasion of the tumour capsule, surrounding soft tissues, blood vessels, or lymphatics. The colour of the mass varies from brown, orange, or yellow depending on the lipid content of the cells.[7] Since ACC is a rare condition with special variants (paediatric, oncocytic, myxoid, and sarcomatoid) histopathological challenges encountered include differentiation of adrenocortical from adrenomedullary tumours, as well as adrenocortical adenomas from carcinomas.[26] There are no clear-cut pathognomonic histological features for a carcinoma; thus, a combination of multiple features are used to diagnose ACC. The Weiss scoring system is widely used, which is based on 9 morphological parameters on light microscopy: 3 each for tumour structure (diffuse architecture, confluent necrosis, clear cells), cytological features (nuclear atypia, mitotic index, atypical mitoses), and invasion (sinusoidal, venous, capsular) (Table 1). It is established that a Weiss score of ≥3 indicates an ACC, whereas scores between 0 and 2 define an adenoma.[27,28]

The Ki-67 labelling index (Ki-67 LI), a marker of proliferation, plays a pivotal role in differential diagnosis of adrenocortical carcinomas from adenomas, with a cut-off value of 2.5–5.0%, although a cut-off of 5% was reported to yield high sensitivity (87.5%) and specificity (97.5%). It is also one of the important prognostic indicators of survival in ACC patients, with a value of >10% leading to shorter overall survival (OS) and more recurrences.[29] As ACCs show significant intratumoural heterogeneity, the Ki-67 LI in 'hot spots' is significantly higher than that in average areas, by both manual and digital image analyses. In addition, it correlates with the Weiss criteria (oeosinophilic cytoplasm, nuclear atypia, atypical mitoses, and sinusoidal invasion).[30]

Staging

The tumour, lymph node, and metastasis (TNM) classification system, proposed by ENSAT, is used to assess the local extension of primary tumours, lymph node involvement, and the presence of distant metastasis (Table 2). Both the Weiss system and TNM staging are useful in predicting the prognosis of ACCs and correlate with each other, with patients at TNM Stages III and IV having a high Weiss score.[31]

TREATMENT

Surgery

The treatment of ACC requires a multidisciplinary management, and surgery is the key therapeutic option that offers a possibility of cure for resectable ACCs: either open adrenalectomy (OA), or minimally invasive surgery. Therefore, staging prior to surgery

is essential to rule out invasion of adjacent organs and distant metastases as one-third of patients present with distant metastases, especially lung and liver.[11] Based on a retrospective study of 201 patients who underwent adrenalectomy for primary ACC, there is no difference in R0 (negative resection margin) status, tumour recurrence, intraoperative tumour rupture, evidence of microvascular or capsular invasion, overall morbidity, or complications between minimally invasive surgery and OA.[32] Similarly, a meta-analysis of data from nine retrospective case-control studies reported no difference in the overall recurrence rate, time to recurrence, cancer specific mortality between open and laparoscopic adrenalectomy. ACCs treated laparoscopically were of small size and more localised (Stage I–II) than OA. Laparoscopic adrenalectomy can offer a shorter hospital stay and a faster recovery; however, it is associated with higher development of peritoneal carcinomatosis (that may possibly be attributed to violation of the tumour capsule during manipulation).[33]

Complete surgical resection is critical in the management of ACCs and approximately two-thirds to three-quarters had lymph node involvement in autopsy studies.[34,35] Moreover, regional lymph node metastasis is an established predictor of poor long-term outcome; however, routine lymphadenectomy during surgical resection of ACC is not commonly performed and its therapeutic role remains controversial. In a multi-institutional study of 120 ACC patients undergoing complete RO resection, peritumoural lymph node dissection (performed in 27%) was independently associated with improved OS. For the study peritumoural lymph node dissection was performed in 27% and associated with large tumours, macroscopically involved lymph nodes, or invasion of adjacent organs.[36] Similarly, in a study from the German ACC registry of 283 non-metastatic ACC patients who underwent complete, margin-negative resection, lymphadenectomy was performed in 17% of cases, and was associated with improved disease specific survival.[37] On the contrary, a larger population study of data from 18 registries involving 1,525 patients failed to prove the survival benefit of lymphadenectomy, performed in 8% of the population. However, lymphadenectomy should be considered in patients with locally advanced tumours (T3 and T4) which have a higher rate of lymph node metastasis.[38]

Debulking surgery is utilised for the removal of large tumours with mechanical signs and to reduce hormone excess; however, the median survival is <12 months.[13] Between 30% and 40% of ACC are metastatic at the onset, and surgical treatment of liver or lung metastasis is associated with long-term survival.[39,40] Recurrence of ACC is relatively common even after curative resection and can be detected in 40–65% within 2 years with a median time to recurrence of 19 months.[41] Repeat curative-intent resection for recurrent ACC in carefully selected patients with two or more factors (solitary tumour, disease-free interval >12 months, and locoregional or pulmonary recurrence) could result in a favourable long-term survival.[42]

Mitotane

Mitotane (Lysodren®, o,p'-DDD) is an adrenocorticotropic drug used for adjuvant therapy after surgical resection, for primary therapy of unresectable cases, and for advanced ACC as a single treatment or in combination with chemotherapy.[6] The 2012 European Society for Medical Oncology (ESMO) guidelines recommend adjuvant mitotane therapy in high-risk surgically treated patients, defined as Stage III, Ki-67 LI >10%, R1 or Rx resection. However, it is not mandatory for low-risk patients with Stage I or II, R0 resection and Ki-67 LI ≤10%.[43] Adjuvant mitotane is routinely started within 3 months of surgery with appropriate monitoring of blood levels and titrating the dose to a concentration of 14–20 mg/L.[2] A recent retrospective analysis demonstrated that blood mitotane concentrations of ≥14 mg/L were associated with a prolonged recurrence-free survival in patients receiving mitotane adjuvant therapy following macroscopically radical surgery.[44] Side effects include gastrointestinal upset, elevation of liver function tests, leucopenia, and confusion.[45]

Radiotherapy

The role of adjuvant radiotherapy in ACC is unclear and the benefits or recommendations cannot be well established due to the lack of prospective large studies. In a retrospective study, radiotherapy prolongs 5 year recurrence-free survival, with no effect on OS and disease-free survival.[46] Another study showed no difference in local recurrence-free rate at 5 years between surgery with adjuvant radiotherapy and surgery alone.[47] Radiotherapy was associated with a 4.7-fold reduction in the risk of local failure compared to treatment regimens without radiotherapy.[48] Thus, adjuvant radiotherapy should be considered in patients with incomplete, R1, or Rx resection, who are at high risk for local

recurrence.[13] CyberKnife® treatment, a stereotactic radiosurgery which deliver high-dose radiation beams to tumours with extreme accuracy, can also be safe and effective for advanced adrenocortical carcinoma, though there are only a few case reports currently available for this option.[49]

Chemotherapy

According to the first international randomised trial in locally advanced and metastatic adrenocortical carcinoma treatment (FIRM-ACT trial), patients who received mitotane plus a combination of etoposide, doxorubicin, and cisplatin (M-EDP) had a higher response rate than those in the streptozocin-mitotane group (23.2% versus 9.2%), although there was no significant difference in the OS.[50] For failed cases with M-EDP, second-line chemotherapy using a combination of gemcitabine and capecitabine is proposed which leads to disease stabilisation for at least 6 months in 29% of patients.[51]

Targeted Therapy

Trials on monoclonal antibodies against various angiogenic receptor tyrosine kinases, such as bevacizumab, sorafenib, sunitinib, and axitinib, yielded disappointing results. Similarly, inhibitors of epithelial growth factor receptor (erlotinib and gefitinib) and IGF-1 (linsitinib, cixutumumab) are not promising in ACC. Recently, novel agents to target steroidogenic factor-1, mTOR, and Wnt signalling pathways have been developed. Inhibitors of acetyl-coA cholesterol acetyl transferase 1, an enzyme for intracellular cholesterol handling, have gained some interest as a potential therapy. With trials underway, these novel targeted agents might be useful for clinical applications in the future.[52]

PROGNOSIS

Even after complete surgical resection with negative margins, the rate of recurrence is high with a 5-year survival rate of 32–45%.[53,54] In a recent study completed in 13 institutions in the USA over a 20-year period, from 1993–2014, there were 49 5-year survivors (27%) and 12 10-year survivors (7%) among 180 patients who underwent resection for ACC. The factors associated with early mortality include positive margins, capsular invasion, distant metastasis, and vena cava involvement.[55]

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INCIDENTALLY DETECTED RENAL ARTERIOVENOUS MALFORMATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Renal arteriovenous malformations and fistula are an uncommon, underdiagnosed condition that can be asymptomatic. However, there is a real risk of rupture and severe bleeding. Imaging techniques have a critical role in planning the treatment. Arteriography is the gold standard but is invasive. Diagnostic selective arteriography can be followed by embolisation of the lesion during the same procedure. Although invasive, because of the potential risk for rupture, arteriography is the elective technique when intervention is planned.

We report a rare case of an adult male patient incidentally diagnosed with arteriovenous malformation. Since he had no prior history of renal intervention or trauma, a diagnosis of idiopathic renal arteriovenous malformation was made. We describe the computed tomography findings and management outcome. This asymptomatic, though potentially lethal, condition can be treated with minimally invasive methods.

Keywords: Arteriovenous malformation, arteriovenous fistula, renal, asymptomatic, idiopathic.

INTRODUCTION

Renal arteriovenous malformation (RAVM) is a rare entity, with an estimated prevalence of <0.04%.[1] Acquired communications between renal arteries and veins are defined as arteriovenous fistulas (RAVF) and are usually secondary to needle biopsy of the kidney or trauma. Conversely, arteriovenous malformations are rare congenital or idiopathic malformations.[2] Cho and Stanley[1] classified the malformations into three types according to angiographic morphology: Type I, a single or a few arteries (fewer than four) shunted into a single draining vein; Type II, multiple arterioles shunted into a single draining vein; and Type III, multiple shunts between the arterioles and venules, forming a complex vascular network. Type III can be further subdivided into two types, according to the size of the fistulous channels (IIIa, nondilated; IIIb, dilated).[1]

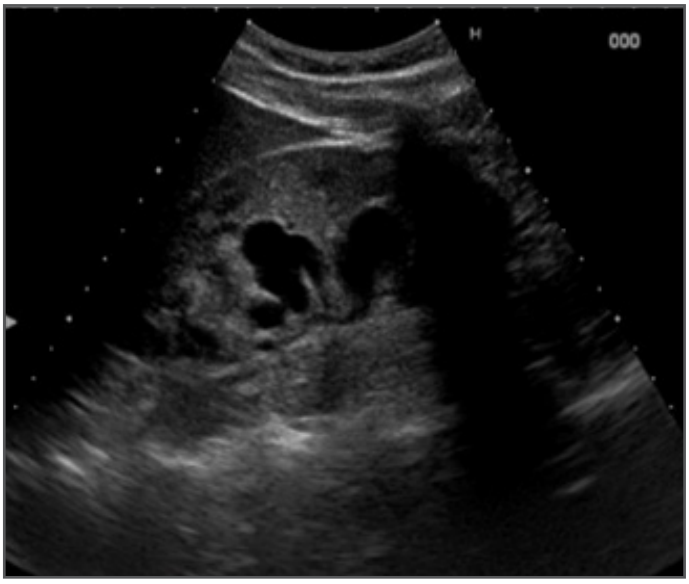

Figure 1: Ultrasound showing an anechoic cavity in the right renal kidney.

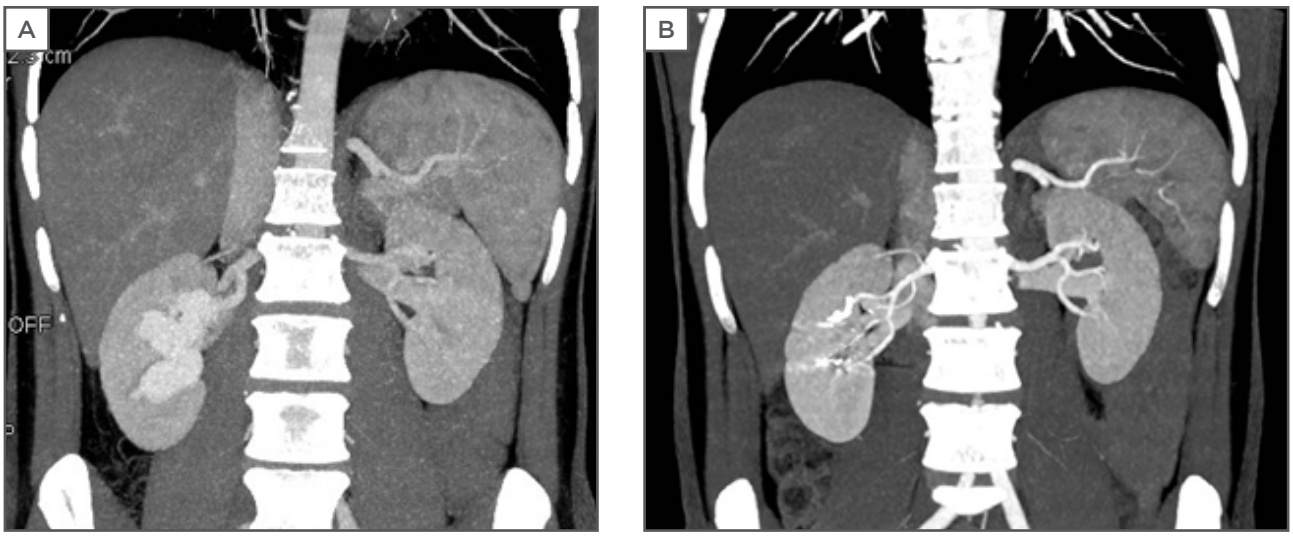

Figure 2: A) Computed tomography angiography reveals the arteriovenous malformation; B) Postoperative computed tomography angiography.

The malformations are classified as congenital, acquired, and idiopathic,[3] or intra and extrarenal.[4] More than 70–75% are acquired, caused by trauma, malignancy, inflammation, or iatrogenesis and consist of a single, tortuous dilated artery communicating with a vein as an aneurysmal fistula (RAVF).[5] About 14–27% of cases are congenital and 2.8% are considered idiopathic (RAVM). The latter are probably caused by fibromuscular dysplasia, which results in arteriovenous communication.[6] Angiographic features have been traditionally used to classify them as either cirsoid or aneurysmal type. The cirsoid type has a knotted, tortuous appearance comprising numerous vessels and multiple arteriovenous (AV) interconnections. The aneurysmal type is a direct RAVF without nidus-like components, which are often associated with aneurysmal dilatation of the feeding artery and/or draining veins.[7] In general, congenital lesions typically have a cirsoid appearance, and acquired or idiopathic lesions are usually aneurysmal.[8]

We report a rare case of an asymptomatic, adult male patient diagnosed with a RAVM, describing the computed tomography (CT) findings and management outcome.

CASE REPORT

A 43-year-old male presented with a urinary tract infection and lower urinary tract symptoms after drainage of a perineal abscess. There was no haematuria, no hypertension, and renal function was normal with a serum creatinine of 0.88 mg/dL and a glomerular filtration rate of >90 mL/min/1.73m^2. Medical history contained severe haemophilia Type A (Factor VIII <1%).

He had a 39˚C fever. Urine cultures showed growth of *Escherichia coli* and *Proteus* species, both sensitive to quinolones. After treatment with antibiotics, his complaints disappeared. There was no pneumaturia nor transanal urinary leakage. Rectal examination was normal. The urinary system ultrasound examination revealed however, a large anechoic cavity located in the right renal pelvis sprouting in different calices (Figure 1). The patient did not report any history of renal trauma or recent medical intervention in which percutaneous instrumentation was used.

On colour Doppler ultrasound, the lesion showed turbulent high blood flow. The patient underwent a CT angiography (Lightspeed VCT 64-Slice, GE Healthcare, Chicago, Illinois, USA). An unenhanced CT was performed of the total abdomen. We started the arterial phase of the kidneys at 100 HU. We administered 120 cc of contrast (Xenetix 350/water) at a flow rate of 3 cc/seconds followed by 20 cc of water at a flow rate of 2 cc/seconds. Then we performed the venous phase of the kidneys and after 300 seconds a delayed phase of the abdomen was performed. The CT angiography demonstrated an aneurysmal type of arteriovenous malformation in the right kidney (Figure 2A).

Because of the size of the malformation and with his medical history of haemophilia in mind, we decided to carry the patient immediately into

the angiography room for endovascular treatment (Allura Xper FD20/10, Phillips, Amsterdam, Netherlands). This procedure in elective conditions has less risk of major bleeding than in an urgent setting.

Selective right renal artery angiography was performed using a 5 Fr 11 cm Arrow-Flex® sheath (Teleflex Incorporated, Wayne, Pennsylvania, USA) with a 0.035 inch Terumo Angled guidewire coupled with a 5 Fr Cobra Glidecatheter (Terumo Corporation, Tokyo, Japan). The lesion was selectively catheterised with a microcatheter (Progreat 2,7F, 0,0025" Terumo Corporation) and embolised with microcoils (Tornado® MWCE-18S-7/3, 18S-8/5, 18S-6/2, 18S-5/2 and18S-10/4, Soft Platinum MWCE-18S-5.2-12-B, Cook Medical, Bloomington, Indiana, USA; AZUR Hydrocoil-18 D2 L20 45-280202, Terumo Corporation). The embolisation was successfully performed (Figure 3A and 3B). The patient's haemodynamic parameters, such as blood pressure, were monitored. He was discharged the following day. Postoperative follow-up was uneventful. The kidney function was still preserved with a serum creatinine of 0.82 mg/dL and a glomerular filtration rate of >90 mL/min/1.73m^2 and CT angiography (Figure 2B) showed no persistent lesion.

DISCUSSION

RAVMs represent an abnormal communication between the renal arterial and venous system.[9] A malformation is usually located in the collecting system and not in the renal parenchyma, with most of the cases on the kidney upper pole (45%), but it also can be detected in the mid-point or in the kidney lower pole in an equal ratio.[10] The left kidney is more frequently involved, and women are affected twice as often as men. The peak incidence is in patients aged 30–40 years, and RAVMs are rare in the paediatric population.[11] The first intrarenal fistula was reported by Vorela in 1928.[4] Surgery, whether nephrectomy or ligation of feeding vessels, has long been the standard treatment for symptomatic arteriovenous malformations or fistulas. The current therapeutic goal for RAVF is to cure arteriovenous shunting but preserve most or all kidney function on the involved side.[5] As an alternative to surgery, percutaneous procedures are becoming widely accepted.[12,13]

RAVMs can be asymptomatic, but may manifest with haematuria, flank pain, flank bruit, hypertension, perinephric haematoma, and high-output heart failure.[7] Although our patient was recently diagnosed with a urinary tract infection after perineal abscess drainage, we believe this infection is related to the intervention rather than caused by the malformation and so he can be classified as an asymptomatic case.

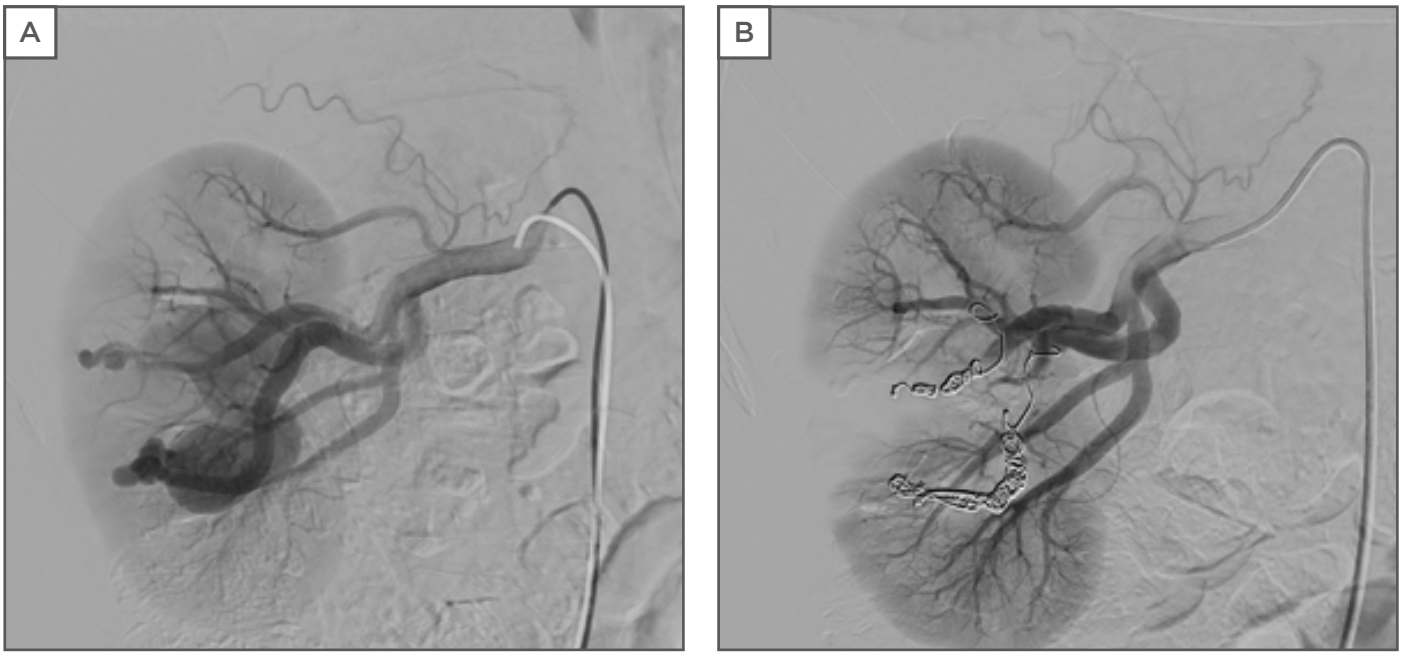

Figure 3: A) Selective arteriography of the right renal artery reveals the arteriovenous malformation; B) Result after selective embolisation of the arteriovenous malformation.

Table 1: Cases of asymptomatic renal arteriovenous malformation.

Author	Number of patients (N)	Age (years)/sex	Indication for study	Diagnostic method	Treatment	Outcome
Tarmiz et al.[14]	1	48/M	Routine follow-up	US	Nephrectomy	Uneventful
Zhang et al.[15]	20, 12 asymptomatic	Not mentioned	Not mentioned	US, CT, and MRI	7 out of 12 with embolisation	Uneventful
Perkov et al.[16]	1	31/M	Follow-up tests	CT	Embolisation	Uneventful
Eom et al.[17]	24, 7 asymptomatic	Mean 45/9M, 15F	Not mentioned	US and CT	Embolisation	Uneventful
Di Vece et al.[2]	1	71/F	Routine US examination	US	Not mentioned	Not mentioned
Nagumo et al.[18]	1	39/M	Routine follow-up	CT	Embolisation	Uneventful
Uchikawa et al.[19]	6, 1 asymptomatic	58/F	Not mentioned	Not mentioned	Embolisation	Uneventful
Thorlund et al.[20]	2	Not mentioned/M	Not mentioned	Not mentioned	Embolisation	Uneventful
Mancini et al.[21]	1	46/M	Follow-up cyst	US	Embolisation	Uneventful
Hermans et al. (mentioned in article)	1	43/M	Routine US examination	US	Embolisation	Uneventful

F: female; M: male; CT: computed tomography; US: ultrasound; MRI: magnetic resonance imaging.

A search of the English language literature using the MEDLINE® database via PubMed revealed only a few asymptomatic cases of RAVM during the last 10 years (Table 1). We excluded all symptomatic cases such as haematuria, hypertension, heart failure, renal failure, or flank pain, and the cases with prior history of renal intervention.

Treatment consists of surgical excision or less invasive intravascular procedures. Surgical treatment (such as partial nephrectomy, total nephrectomy) renal auto-transplantation or vessel ligation, is recommended for malformations of >2cm in diameter in women of childbearing age, with an expanding size on serial angiograms, with an incomplete ring like calcification on radiography, in the presence of uncontrollable hypertension, or in the presence of high output heart failure.[22] This hypertension is renin-mediated hypertension caused by fistula-related relative ischaemia; the high-output cardiac failure can be explained by an increase in venous return.[23] In order to avoid nephrectomy, reduce preoperative risk, and shorten hospital stay, transarterial embolisation may be regarded as the first-line treatment of RAVM.[10]

There exist several embolic materials, including particles (gelatine sponge particles and polyvinyl alcohol particles), coils (pushable and detachable coils), vascular plugs, detachable balloons, and liquid materials (absolute ethanol, N-butyl-2-cyanoacrylate, and ethylene vinyl alcohol copolymer [Onyx®]). The appropriate selection of the embolic material is based on the type of RAVMs and the size and flow of the lesion.[7] Embolisation of high-flow RAVMs can be technically difficult because the torrential flow through these lesions increases the risk of loss of the embolic device into the pulmonary circulation.[24]

Transcatheter arterial embolisation may sometimes cause post-embolisation syndrome, which consists of fever, loin pain, nausea, and vomiting. Selective embolisation of RAVMs preserves the renal parenchyma and therefore leads to minimal post-embolisation syndrome.[25] Furthermore, there is a risk of recanalisation and/or incomplete occlusion after inadequate or incomplete embolisation.[7] The risk of recanalisation depends on the type of embolic material used and the size of the lesion.[7] Our patient showed no signs of complications related to the procedure.

Estimation of RAVM instability is difficult or impossible to be detected. There are computer methods that provide support to surgeons to

overcome clinical diagnostic limits and help them during the process of medical decision making between invasive or endovascular intervention.[9]

Our patient met the typical diagnostic criteria to treat with an endovascular procedure. Our aim was to treat the RAVM before it became symptomatic. In consideration of the known haematologic medical history, treatment was planned relatively fast after diagnosis, in particular to avoid bleeding and haematuria. The RAVM was coiled successfully. The postoperative period was uneventful, and renal function was preserved. Yearly follow-up with ultrasound will be provided.

CONCLUSION

RAVMs are a rare entity. We presented a case of idiopathic, asymptomatic AV-malformation in a 43-year-old male who underwent an urgent but elective embolisation. There are only a few asymptomatic cases in the literature who were treated. Even though still asymptomatic, treatment must be considered in the light of newly developing, less invasive, endovascular procedures. The general condition of the patient and his or her symptoms must be considered in the therapeutic decision-making. In the past, there were only invasive therapeutic options, but embolisation by selective catheterisation can be considered safe and effective in both elective and urgent cases.

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NEGATIVE BIOPSIES WITH RISING PROSTATE-SPECIFIC ANTIGEN. WHAT TO DO?

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ABSTRACT

Introduction: Prostate-specific antigen (PSA) is the main tool of detection for prostate cancer (PCa). However, PSA has limited specificity and sensitivity in determining the presence of PCa, leading to unnecessary biopsies and the diagnosis of potentially indolent PCa. The aim of this article is to review the tools available to urologists in the clinical situation of rising PSA with prior negative biopsies.

Evidence synthesis: The need for prostate biopsy is based on PSA level and/or a suspicious digital rectal examination. Ultrasound-guided biopsy is the current gold standard. The incidence of PCa detected by saturation repeat biopsy is 30–43%. Prostate health indes, prostate cancer antigen 3, and 4Kscore are available second-line tests to distinguish between malignant and benign prostate conditions, reducing the number of unnecessary biopsies. Molecular testing including ConfirmMDx (MDxHealth, Irvine, California, USA) and The Prostate Core Mitomic Test™ (PCMT) (MDNA Life Sciences, West Palm Beach, Florida, USA) are tissue tests for men with prior negative biopsy. Multiparametric magnetic resonance imaging (mpMRI) is used for lesion identification and subsequently for biopsy or treatment. In the setting of suspected PCa, the use of prostate mpMRI has shown to have a negative predictive value for clinically significant PCa of 80–96%.

Conclusions: Approximately 70% of patients undergoing prostate examination will have a negative result following analysis of the biopsy sample. This negative diagnosis leads to the common clinical challenge of determining when and if a repeat biopsy should be performed. New blood, urine, tissue, and imaging tools are now available to guide this decision.

Keywords: Prostate cancer (PCa), negative prostate biopsies, biomarkers, tissue markers, multiparametric magnetic resonance imaging (mpMRI), prostate-specific antigen (PSA).

INTRODUCTION

Prostate-specific antigen (PSA) testing is the main tool of detection for prostate cancer (PCa).[1] However, PSA has limited specificity and sensitivity in determining the presence of PCa, leading to unnecessary biopsies and the diagnosis of potentially indolent PCa. Additional information may be gained by the Progensa DRE urine test (Hologic, Marlborough, Massachusetts, USA) for prostate cancer antigen 3 (PCA3), the serum 4Kscore and Prostate Health Index (PHI) test, or a tissue-based epigenetic test (ConfirmMDx). The current diagnostic procedure for men with suspected PCa is ultrasound-guided biopsy. For a prostate volume of 30–40 mL, >8 cores should be sampled; 10–12 core biopsies are recommended. Unlike many other solid tumours, for which image-guided biopsy is common, PCa has

traditionally been detected by randomly sampling the entire organ. However, the recent introduction of multiparametric magnetic resonance imaging (mpMRI) allows for image-based identification, which may improve diagnostic accuracy for higher risk tumours. Advances in imaging have led to the development of fusion biopsy platforms in which mpMRI images are electronically superimposed in real time on transrectal ultrasound (TRUS) images. Numerous targeted biopsy platforms exist and can perform biopsies of suspicious regions seen on the prostate mpMRI.[2-6] The aim of this article is to review the available tools for the urologist in the clinical situation of rising PSA with prior negative biopsies.

INDICATION FOR REPEAT PROSTATE BIOPSY

Current Role of Saturation Biopsies in Prostate Cancer

The need for prostate biopsy is typically based on PSA level and/or a suspicious digital rectal examination (DRE). Age, comorbidity, patient preference, and therapeutic consequences should also be considered and discussed beforehand. Risk stratification is a potential tool for reducing unnecessary biopsies. A single PSA elevation alone should not prompt immediate biopsy and the PSA level should be verified after a few weeks in the same laboratory. Empiric use of antibiotics in an asymptomatic patient to lower the PSA should not be undertaken.[7,8]

Ultrasound-guided biopsy is the current gold standard. The TRUS approach is used for most prostate biopsies although some urologists instead use a transperineal approach. PCa detection rates are comparable with both techniques according to two prospective randomised trials. Recently Scott et al.,[9-11] in a retrospective cohort of 431 radical prostatectomy specimens, concluded that the transperineal approach predicted with more accuracy the clinical risk category than the TRUS approach. A higher level of evidence is needed to support these findings.

The actual indications for repeat biopsy include:

- Rising and/or persistently elevated PSA
- Suspicious DRE, 5–30% PCa risk
- Atypical small acinar proliferation, 40% risk
- Extensive (multiple biopsy sites, i.e. >3) high-grade prostatic intraepithelial neoplasia, 30% risk
- Positive mpMRI findings

Table 1: Overview of biomarkers of prostate cancer.

Sample	1st biopsy	Repeat biopsy	Description
Serum	PSA	PSA	PSA
Serum	PHI	PHI*	Total PSA, [−2]proPSA, free PSA
Plasma	4Kscore	4Kscore	Total PSA, free PSA, intact PSA
Urine (after DRE)	PCA3	PCA3*	PSA and PCA3 mRNA

*Approved by US Food and Drug Administration (FDA).
PSA: Prostate-specific antigen; PHI: Prostate Health Index; PCA3: prostate cancer antigen 3; DRE: digital rectal examination.

The incidence of PCa detected by saturation repeat biopsy (>20 cores) is 30–43% and depends on the number of cores sampled during earlier biopsies. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The high rate of urinary retention (approximately 10%) is a drawback.[12]

Biomarkers (Table 1)

Screening, over-diagnosis, and over-treatment are topics of debate in PCa. There is a need to differentiate between clinically significant and indolent cancer, and PSA has been shown not to be the best marker to solve this issue. The ideal PCa biomarker would be capable of distinguishing PCa from benign prostate conditions and differentiating between aggressive and indolent tumours. Patients with a prior negative biopsy and persistently high PSA, especially in the grey area (4–10 ng/mL), represent a challenge and a controversial topic in which there is not currently consensus.[13-15]

Accordingly, only 20–30% of men with serum PSA levels from 2–4 ng/mL and 30–45% with serum PSA levels from 4–10 ng/mL have PCa diagnosed on prostate needle biopsy. To address these limitations, adjunctive measurements, including the ratio of free-to-total PSA, called percent-free PSA, have been investigated and shown to significantly improve cancer detection rates within the 4–10 ng/mL range.[16-18]

More recently, distinct molecular forms of free PSA have been characterised and found to be differentially associated with benign prostatic hyperplasia (BPH) or PCa. These precursor forms

of PSA are enzymatically inactive and include: i) proPSA, which is elevated in cancer tissue and serum, as well as ii) benign PSA (BPSA), and iii) intact PSA, which are associated with BPH. The [–2] proPSA isoform has emerged as a promising marker for PCa detection, as it is preferentially concentrated in cancerous tissue on histochemical staining.[19]

Prostate Health Index

The PHI blood test combines the relative concentrations of three different PSA forms: total PSA, free PSA, and [–2]proPSA, using a mathematical formula: ([–2]proPSA/free PSA) × √PSA. It was developed by Beckman Coulter in partnership with the National Cancer Institute (NCI) Early Detection Research Network (EDRN) and approved by the US Food and Drug Administration (FDA) in 2012. The 2016 National Comprehensive Cancer Network (NCCN) guidelines offer PHI as an option to increase specificity before initial or repeat biopsy, and has regulatory approval in >50 countries.[20-22]

PHI has been consistently shown to outperform PSA to distinguish malignant and benign prostate conditions in men with a PSA level >2 and/or a suspicious DRE. Several studies have demonstrated that PHI significantly improves PCa detection in high-risk cases and also predicts the aggressiveness of disease. In the clinic, PHI is less expensive than other tests such as the 4Kscore or PCA3, and does not require a physician to conduct a DRE, making it logistically attractive for both clinicians and patients.[13]

Recently, Loeb et al.[23] developed a nomogram using continuous values of PHI as part of a multivariable model which improves the prediction of aggressive PCa among individual patients with PSA between 2–10 ng/mL and benign DRE. PHI predicted the risk of aggressive PCa across the spectrum of values. Adding PHI significantly improved the predictive accuracy of the risk calculators for aggressive disease. A new model was created using age, previous biopsy, prostate volume, PSA, and PHI, with an area under the curve (AUC) of 0.746. The bootstrap-corrected model showed good calibration with an observed risk for aggressive PCa and had net benefit on decision-curve analysis.[23]

Another recent study combining PHI and mpMRI in men requiring repeat biopsy explored the potential value of the PHI in the context of image-guided repeat biopsies. In this study, adding PHI to mpMRI improved overall and significant cancer prediction (AUC 0.71 and 0.75) compared to mpMRI + PSA alone (AUC 0.64 and 0.69, respectively). At a threshold of ≥35, PHI + mpMRI demonstrated a negative predictive value (NPV) of 0.97 for excluding significant tumours. In mpMRI negative men, the PHI again improved the prediction of significant cancers; AUC 0.76 versus 0.63 (mpMRI + PSA). Using a PHI ≥35, only 1/21 significant cancers was missed and 31/73 (42%) men were potentially spared a re-biopsy (NPV of 0.97, sensitivity 0.95). In this way, the authors proposed PHI adds predictive performance to image-guided detection of clinically significant cancers and has value in determining the need for re-biopsy in men with a negative mpMRI.[24]

Prostate cancer antigen 3

PCA3 was described initially by Bussemakers et al.[25] in 1999. PCA3 score measures the ratio of PCA3 and PSA mRNA in the urine after vigorous DRE using transcription-mediated amplification.[25,26] PCA3 was approved by the FDA in 2012 for men with a previous negative biopsy and a persistently elevated PSA level to aid in decision-making regarding repeat biopsies and was also an option mentioned in the 2016 NCCN guidelines. Although PCA3 can be offered to patients with a previous negative biopsy, its clinical effectiveness for this purpose is uncertain. In addition, its relationship to cancer aggressiveness is subject to debate and generally inferior to other markers.

Ferro et al.[27] compared PHI with PCA3 in patients who were undergoing initial biopsy and found that PHI and PCA3 had a similar predictive accuracy for overall PCa detection; AUC of 0.77 for PHI and 0.73 for PCa and that both tests outperformed percentage-free PSA. In another study, PCA3 had similar predictive value for PCa in candidates for repeat biopsy compared to PHI (AUC 0.77 versus 0.69).[27]

In the repeat biopsy setting, there were also opposing results with no statistically significant differences between PHI and PCA3. Perdona et al.[28] evaluated the use of a combination of PCA3 and PHI in predicting biopsy results in 160 men upon initial biopsy. Receiver operating characteristic (ROC) analyses showed that PHI outperformed PCA3 for high specificity level, whereas PCA3 outperformed PHI for high sensitivity level.[28] On the other hand, Ferro et al.[27] showed that PHI and PCA3 were the strongest predictors of PCa with no significant differences in pairwise comparison.

Table 2: Tissue markers of prostate cancer.

Tissue markers	Description	Clinical use
ConfirmMDX®	Epigenetic test. Monitors the methylation states of *APC*, *GSTP1*, and *RASSF1* (altered in prostate cancer).	Assays use core specimens following a negative diagnosis on analysis of a primary biopsy sample.
Prostate Core Mitomic Test™	Tests for a single 3.4 kb mitochondrial DNA deletion.	Assays detect altered mitochondrial DNA from prostate tissue associated with cancer.

APC: adenomatous polyposis coli; *GSTP1*: glutathione Stransferase pi 1; *RASSF1*: Ras association domain family member 1.

The combination of the two tests did not further improve diagnostic power in this cohort.

Many studies show that PCA3 is inferior for identifying high-grade disease compared to PHI. Seisen et al.[29] found that PCA3 detected more PCa overall than PHI when cut-off scores for positive results were set at >35 for PCA3 and >40 for PHI, but had worse performance than PHI for identifying clinically significant disease.

Ferro et al.[30] found that PCA3 and PHI levels were significantly higher in patients with tumour volume ≥0.5 mL, pathological Gleason ≥7, and pT3 disease (all p values ≤0.01). ROC curve analysis showed that PHI is a better accurate predictor of high-stage (AUC 0.85 [0.77-0.93]), high-grade (AUC 0.83 [0.73-0.93]), and high-volume disease (AUC 0.94 [0.88-0.99]) than PCA3, who showed lower AUCs, ranging from 0.74 for Gleason to 0.86 for tumour volume.[30]

4Kscore

The 4Kscore is a risk calculator for the detection of PCa on biopsy, based on the 4-Kallikrein panel combined with patient age, DRE, and biopsy history. The 4-Kallikrein panel includes total PSA, free PSA, intact PSA, and hK2, a kallikrein with high homology with PSA responsible for the *in vitro* cleavage of proPSA, resulting in the 'mature' form of PSA. The 4Kscore provides probability of having high-risk PCa. Although the 4Kscore does not have FDA approval, the 2016 NCCN guidelines also offer this as a second-line testing option for patients who have never undergone biopsy or after a negative biopsy.[22]

The 4Kscore is associated with an improvement of 8–10% in predicting biopsy-confirmed PCa, indicating that the use of the 4Kscore could potentially reduce the number of prostate biopsies currently conducted by an estimated 48–56%.[31]

Tissue Markers (Table 2)

Sampling errors inherent with the random tissue collection of the biopsy procedure result in a false-negative rate of approximately 25%. This imprecision poses a diagnostic dilemma, often resulting in multiple repeat biopsies. Although diminishing rates of cancers are detected during these invasive repeat procedures, a high rate of clinically significant (i.e. a Gleason score ≥7) cancer is still on the second, third and fourth or more biopsies (65%, 53%, and 52%, respectively). Molecular testing is another option to help identify occult cancer in this situation.[32-35]

ConfirmMDx

ConfirmMDx[36] is a methylation assay that measures changes in methylation in benign tissue to identify peritumour regions adjacent to missed cancer (termed the 'halo effect'). This test evaluates the methylation patterns of three genes: glutathione Stransferase pi 1 (*GSTP1*), adenomatous polyposis coli (*APC*), and Ras association domain family member 1 (*RASSF1*). Investigators in the MATLOC study[37] specifically examined the ConfirmMDx test by running this assay on core prostate biopsy samples from men with prior negative biopsy.[36,37] After adjusting for patient characteristics, the assay was a significant predictor of repeat biopsy outcome on multivariate analysis (odds ratio [OR]: 3.17; 95% confidence interval [CI]: 1.81–5.53) with a NPV of 90%. A subsequent study of 350 American men demonstrated a NPV of 88% with ConfirmMDx the most significant independent predictor of PCa in repeat biopsy samples (OR: 2.69; 95% CI: 1.60–4.51).[38]

Of note, the presence of atypical features (such as atypical small acinar proliferation on histological examination) was also a significant predictor on multivariate analysis, associated with a two-fold increased risk of PCa diagnosis (OR: 2.11).[38]

Results to date suggest that this new tissue-based assay might help to distinguish between men who are free of PCa and those with occult disease, thereby potentially reducing the use of unnecessary repeat biopsy procedures. It is also included in the 2016 NCCN guidelines as an optional second-line test before repeat biopsy.

The Prostate Core Mitomic Test

PCMT[39] is another field effect laboratory test based on detection of a single 3.4 kb mitochondrial DNA deletion. An early study involving a cohort of 183 men including those with benign, malignant, or pre-malignant biopsy samples, generated a remarkable AUC of 0.87 using this test in the validation phase.

In a follow-up study of 101 patients undergoing repeat biopsy procedures, 20 were found to have PCa within 1 year of the initial biopsy; analysis of biopsy samples for PCa using the PCMT was associated with a sensitivity and specificity of 84% and 54%, respectively, (AUC 0.75) and a negative predictive value of 91%.[40] Larger validation studies are required before the widespread use of this assay can be recommended.

Problems with tissue-based assays include the potentially confounding effects of infection and/or inflammation, age-related changes, the ability to distinguish high-grade from low-grade PCa, and the detection of clinically insignificant PCa. APC methylation patterns are altered in the presence of inflammation in many cancer types.[41] Methylation patterns in histologically normal prostate tissue alter with age, potentially adding additional sources of error that must be considered. Overall, comparative studies are necessary to help guide test selection.

Multiparametric Magnetic Resonance Imaging

mpMRI of the prostate has been an imaging technique available for over two decades. In the past 10 years, there has been an increased interest in the method due to validation of multiple imaging parameters, which when combined can be used in PCa detection and staging.

mpMRI outputs are used by the radiologist for lesion identification or staging and subsequently can be used to perform targeted biopsy and to aid in treatment planning for those men ultimately diagnosed with PCa. The current European Association of Urology (EAU) recommendations outline its primary use in lesion targeting in the setting of a previous negative biopsy and a persistent clinical suspicion of cancer. Additionally, its use is recognised for local staging and in the decision process of whether to perform nerve-sparing surgery in the setting of intermediate or high-risk disease.[1] A recent consensus statement from the American Urological Association (AUA) and Society of Abdominal Radiology (SAR) concluded that patients receiving a prostate imaging reporting and data system (PI-RADS) assessment category of 3–5 warrant repeat biopsy with image-guided targeting.

While TRUS-guided MRI fusion or in-bore MRI targeting may be valuable for more reliable targeting, in the absence of such targeting technologies, cognitive (visual) targeting remains a reasonable approach in skilled hands. At least two targeted cores should be obtained from each MRI-defined target. Given the number of studies showing a proportion of clinically significant cancers missed by MRI targeted cores, a case-specific decision must be made on whether to also perform concurrent systematic sampling. However, performing a solely targeted biopsy should only be considered once quality assurance efforts have validated the performance of prostate MRI interpretations with results consistent with the published literature. If a repeat biopsy is deferred based on MRI findings, then continued clinical and laboratory follow-up is advised and consideration should be given to incorporating repeat MRI in this diagnostic surveillance regimen.[2]

In the setting of suspected PCa and previous negative biopsy, the use of prostate mpMRI has shown to have a NPV for a clinically significant PCa of 80–96%.[3-6] Its use in this cohort is primarily by planning a mpMRI targeted biopsy, which has been demonstrated to detect more clinically significant cancers and fewer clinically insignificant cancers than a systematic biopsy.[6] The best fusion biopsy method and approach is still strongly debated, with vendors offering either a TRUS or transperineal biopsy approach. That notwithstanding, fusion biopsy appears to improve sampling efficiency for clinically significant disease regardless of the platform.[2,42]

Image reporting has been standardised in 2012 with the PI-RADS classification, later revised in 2015 as Version 2.[43,44] Image acquisition is recommended to be performed on a high-field magnet (≥1.5 tesla), with or without the use of an endorectal coil.[44] Interpretation is performed based on three imaging sequences: T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast enhancement (DCE).

T2-weighted imaging is used to delineate prostate anatomy, identify suspicious areas of clinically significant PCa, and assess extracapsular extension.[1] Current PI-RADS recommendations consider it the dominant sequence in lesion scoring in the transition zone of the prostate, with about 30% of PCa occurring in this region.[45] In the peripheral zone, PCa is seen as a mass-like low signal lesion, but this appearance has a low specificity and is considered insufficient on its own, which led to the addition of DWI.[46]

DWI allows for the measurement of water movement through a tissue voxel. A high signal indicates slower water diffusion through tissue indicating a high cell count or tissue swelling. Due to the higher mitotic rates of neoplastic cells, areas with PCa cells may be visible as bright areas (i.e. areas of restricted diffusion). This is useful in the homogenous peripheral zone of the prostate, where >70% of cancers are detected.[45] For this reason, the dominant sequence for assessment of the peripheral zone is DWI. This sequence is technically difficult to obtain well, being dependent on multiple factors, which has led to the addition of DCE imaging to the diagnostic protocol.

Contrast administration is acquired as a dynamic sequence, allowing for the registration of temporal contrast curves. The reviewed PI-RADS guidelines have decreased the diagnostic importance of focal enhancement. Currently, DCE is used to further characterise lesions of undetermined significance in the transitional zone (PI-RADS 3). The additional finding of enhancement of these lesions increases the lesion probability to PI-RADS 4, and its influence on scoring is binary. The use of gadolinium is currently debated, and may be of less importance in future guidelines.[47,48]

Prostate mpMRI has emerged as an effective diagnostic tool used in PCa detection and subsequently may help with staging for those men ultimately diagnosed with PCa. Its use is facilitating a shift from the traditional PSA-TRUS biopsy pathway to a patient-centred model according to the tumour location and stage, making its applications invaluable.

CONCLUSIONS

Approximately 70% of patients who undergo prostate biopsy will have a negative result. This negative diagnosis leads to the common clinical challenge of determining when and if a repeat biopsy should be performed, and which tools should be used to guide this decision. Despite all the current evidence, no recommendation can be made regarding the best biomarker to use in the setting of repeat biopsies; although PHI, 4Kscore, and PCA3 have added value in the detection of PCa on biopsy. The use of new molecular diagnostic technologies, such as epigenetic tests, is another possible way to inform repeat biopsy decisions. Meanwhile, comparative studies are needed to confirm the optimal biomarker to determine which is the most cost-effective marker to use in patient selection for repeat biopsy.

Biomarkers in PCa are a rapidly expanding field and recent developments of proteomic/genomic platforms, as well as the rise of immunotherapy provide meaningful research opportunities for the upcoming years. Other promising innovations, such as imaging biomarkers, are also being developed. Nonetheless, many challenges still lie ahead. In the current clinical practice, before repeat biopsy, the urologist should perform mpMRI when clinical suspicion of PCa persists in spite of negative biopsies, with a 1a level of evidence and grade of recommendation A. A major goal to strive for is refinement of the current biopsy approach by using mpMRI in optimising the detection of significant PCa.

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MANAGEMENT OF ANTERIOR URETHRAL STRICTURES

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ABSTRACT

Anterior urethral strictures affect the male urethra between the tip of the penis and the apex of the prostate. These form the bulk of urethral strictures in men. The common causes for urethral strictures seem to be idiopathic or related to instrumentation of the urethra. Clinically, patients have varying obstructive symptoms associated with the progressive narrowing of the urethral lumen. Treatment modalities have aimed at incising or excising the fibrous tissue, augmenting the damaged area by grafts or flaps, or more recently, replacing the area with tissue engineered constructs. As the biology of wound healing and fibrous tissue formation is not yet completely understood, urethral strictures continue to pose a challenge to clinicians and scientists.

Keywords: Anterior urethral stricture, urethral stricture management, urethroplasty, tissue engineering.

INTRODUCTION

Urethral stricture disease (USD) affects 0.6% of the at-risk male population.[1] Patients present with symptoms such as difficulty in voiding, nocturia, and painful urination, resulting in significantly reduced quality of life.[2] The underlying causes and rates of incidence depend on patient age, race, geography, and socioeconomic status.[1,3-5] Conventional treatments, such as dilatation, urethrotomy, and urethral stent, aim to reverse the progressive narrowing of the lumen. Surgical repair with a buccal mucosal urethroplasty has emerged as a gold standard over the years, with a success rate as high as 95%. However, the procedure is associated with limitations, such as donor site morbidity, longer surgical times, and the recurrence of urethral strictures.[6] Therefore, efforts to deploy acellular scaffolds and tissue engineered urethral substitutes have been made.[7-28]

Firstly, this review aims to outline the epidemiology, aetiology, and pathophysiology of USD. Secondly, conventional methods of USD management are discussed from a clinician's point of view. Lastly, we highlight the state-of-the-art in tissue engineering-based urethral substitutes and outline the potential of tissue engineering in urethral reconstruction surgery.

EPIDEMIOLOGY

The real incidence of urethral strictures is not known, but estimates can be obtained from representative population datasets. Incidence varies based on age, race, geography, and socioeconomic status. The incidence is 1.6 and 10-times higher in older versus younger patients in the USA and UK, respectively.[1,3] Beyond the age of 65 years, incidence steadily increases, peaking with men >85 years old.[4,5] In the USA, African-Americans and Hispanics have a higher incidence of urethral strictures in comparison with Caucasians.[1,5] Urethral strictures are 2.6-times more prevalent in urban centres than in rural ones. In developing countries, the prevalence of urethral strictures is thought to be much higher because of higher rates of infectious and inflammatory strictures,[4,29] and they typically affect a much younger population.[4,30,31]

AETIOLOGY OF URETHRAL STRICTURES

The four main aetiologies of urethral stricture are trauma, inflammation, iatrogenic, and idiopathic.[32]

In developed countries, these strictures account for 15%, 19%, 33%, and 33% of all strictures, respectively.[32] Trauma to the anterior urethra in the form of blunt straddle injury occurs predominantly in the bulbar urethra, resulting in urethral strictures.[33,34] In developed countries, the most common cause for inflammatory strictures is lichen sclerosus (LS), which accounts for approximately 5–14% of urethral strictures.[3,35,36] Iatrogenic strictures are caused typically due to instrumentation and tend to occur frequently in the bulbar urethra.[37] The occurrence of idiopathic strictures is predominantly in the bulbar urethra (88.4%),[37] and is more frequent in younger patients.[3,38] Idiopathic strictures may be due to unrecognised childhood trauma, as it may take years before the manifestation of significant strictures.[39,40] Understanding the aetiology is important as it impacts the stricture location and the success rate of reconstructive surgery.

PATHOPHYSIOLOGY OF THE URETHRAL STRICTURE

Urethral stricture is a fibrotic process initiated by urethral mucosal injury. Epithelial ulceration exposes the corpus spongiosum, leading to spongiofibrosis and resulting in poorly compliant tissue and a diminished urethral lumen.[41] Urethral strictures are characterised by significant changes in the extracellular matrix of the spongiosum, such as an increased number of myofibroblasts, increased collagen deposition, and reduced elastin content.[42-44] The degree of injury and underlying aetiology of the urethral stricture determines the extent of spongiofibrosis.

DIAGNOSIS AND EVALUATION OF URETHRAL STRICTURES

Urethral stricture patients may experience a steady deterioration of the urinary stream, concomitant with lower urinary tract symptoms, such as urinary hesitancy, incomplete bladder emptying, and nocturia.[2,45] Clinical assessments should include history, a clinical examination of the genitalia, and an ultrasound evaluation of the urethra and bladder. Clinically, one can recognise the lichen sclerotic changes, scars, and changes related to previous repairs.[46] A retrograde urethrogram (RUG) provides clinically relevant information concerning the location, length of the stricture, and any associated pathologies.[45] The sensitivity of RUG in the assessment of urethral strictures is approximately 75–100% with specificities in the range of 72–97%.[47] However, RUG does not allow for direct examination of the spongiofibrosis and relies on the examiner to conclude its presence on the basis of intraluminal data.[47] Ultrasound may be more sensitive compared with RUG in determining the stricture length and the degree of spongiofibrosis.[47] Cystoscopy is considered the most specific test to diagnose urethral obstruction.[47]

MANAGEMENT OF URETHRAL STRICTURES

The principle of treatment of urethral strictures is to restore and maintain the luminal diameter for as long as possible. This can prevent obstructive symptoms caused by progressive urethral narrowing, and the complications associated with residual urine. The current treatment modalities available for the management of urethral strictures include dilatation, urethrotomy, and urethroplasty.

Dilatation

Urethral dilatation dynamically extends the urethral lumen by means of dilators that are calibrated in accordance with the French system, in which the dilator size correlates with the urethral circumference in millimetres.[2] Dilators vary from metallic dilators to flexible plastic or polyurethane dilators. The complications associated with dilatation include injury, bleeding, false passage creation, inadequate dilatation, and stricture recurrence.[48] Dilatation may exacerbate spongiofibrosis and therefore, it is not recommended for strictures caused by LS. However, some patients who are not suitable for urethroplasty or reluctant to undergo the procedure may prefer self-dilatation with flexible dilators. This can be continued as long as patients do not suffer from complications. At present, the use of metal dilators is limited to the dilatation of the meatal stenosis and submeatal strictures. Repeated dilatation can make future surgical repair more difficult and less successful.[49]

Urethrotomy

During urethrotomy, an incision is made through the stricture to the healthy underlying tissue to increase luminal calibre.[50] The incision can be made in a blind fashion using an Otis urethrotome, or a direct vision internal urethrotomy (DVIU) with a cold knife or a laser. Urethral tissue tearing is the main risk associated with using the Otis urethrotome. The complications of DVIU include bleeding,

bacteraemia, false passage creation, meatal stenosis, extravasation of fluid into the spongiosum, urinary sepsis, and erectile dysfunction. Strictures with the most promising response to DVIU are short (<1 cm) bulbar urethral strictures with minimal fibrotic narrowing of the lumen. Several methodshave been tried to improve the outcomes of urethrotomy. Laser urethrotomy has been attempted, but has not shown superior outcomes when compared to cold knife urethrotomy.[51] Intralesional injection of medications such as corticosteroids,[52] Mitomycin C,[53] and intraurethral Captropril gel[54] have been used in an attempt to decrease the fibrotic response after DVIU. No long-term follow-up data are available to determine the true benefit of such strategies. Studies have reported leaving the in-dwelling catheter for 1–4 days.[55] However, prolonged duration of the in-dwelling catheter has not reported any superior benefits.

DVIU can be supplemented with the placement of either Wallstent™/Urolume® permanent stents or the Memokath™ temporary stents. The long-term success rate of stents is 85%.[56] The complications associated with stents are stent migration, stenosis, urethral obstruction, and the need for reoperation. Urethral stents are indicated for patients with short (<3 cm) bulbar urethral strictures who are unfit for urethroplasty.[56]

Long-term cure by DVIU is not likely after the third instance of incision/dilatation or in cases where stricture recurrence occurs within 3 months of the first incision. At present, DVIU is used as a maintenance treatment.

Urethroplasty

Urethroplasty is considered the ideal treatment of anterior urethral strictures. The types of urethroplasty available include excision and primary anastomosis (EPA), augmentation and substitution with a dorsal or ventral onlay graft, or a flap. Stricture length, location, pliability of the urethral plate, and lumen of the stricture area dictate the type of urethroplasty. Urethroplasty with the exception of the EPA can be carried out as a single stage or multiple stage procedure, depending on the amount of healthy tissue available at the time of surgery. In order to devise the surgical strategy, anterior urethral strictures can be divided into simple strictures which include strictures of the mucosa with or without spongiofibrosis, of idiopathic aetiology, and complex strictures which include strictures due to LS and failed hypospadias repairs.

Excision and primary anastomosis

EPA is the surgical reconnection of the ends of the urethra after resection of the fibrotic tissue in between. The long-term success of EPA for short (<2 cm) bulbar urethral strictures is around 90–95%, therefore it is recommended for such strictures regardless of aetiology or prior treatment.[57] Complications of EPA include fistula, urinary tract infection, post-micturition dribble, and erectile dysfunction.[57] Incomplete stricture excision and mobilisation of urethra may result in the failure of the treatment.[58]

Augmentation and substitution urethroplasty

For strictures >2 cm in length, the anastomosis is augmented using a buccal mucosa graft (BMG) placed ventrally or dorsally, with a tissue flap if necessary. The BMG is usually obtained from the inside of the cheek, the inferior surface of the tongue, or the inner surface of the lip. Donor site morbidity associated with graft harvesting includes oral numbness and restricted movement of the mouth.[6]

In substitution urethroplasty, the strictured portion of the urethra is replaced with grafts or flaps. Several autologous grafts or flaps from genital and extra-genital skin or mucosa have been used, but BMG is the most popular choice because of ease of graft harvest and surgery. The functional outcomes of skin and BMG are comparable.[59]

However, in the case of LS related strictures with autoimmune aetiology, BMG is the recommended graft because surgical reconstruction using genital skin tends to end in failure. In the case of complex anterior strictures of LS, on the basis of the urethral plate and the extent of luminal obliteration, a 1-stage (Kulkarni or Asopa technique) or 2-stage Johansen procedure is carried out. Dubey et al.[60] showed good results using this 2-stage technique: 22 of 25 patients (88%) had successful outcomes at a mean follow-up of 32.5 months. Kulkarni et al.[61] corroborated these results, reporting a 91% success rate at a mean follow-up of 38 months.

Complications of urethroplasty include post-void dribbling, diverticulum/pouch, urinary tract infection, chordee, urethrocutaneous fistula, impotence, and reoccurrence of strictures.[62,63] In spite of high overall success rates, meticulous urethroplasty technique, and good substitution

material, stricture recurrence has been reported. After substitution urethroplasty, the recurrence has two marked features: fibrosis of the grafted area and fibrous ring strictures at the anastomotic sites.[63] We have a hypothesis to explain this based on our experience with tissue engineering. Upon anastomosing two edges of the tissues, the actual closure happens due to the multiplication of the basal epithelial cells. Therefore, the other layers of the graft and recipient area are not involved in multiplication and become redundant, thereby giving rise to an inflammatory reaction. In the process of expelling the non-multiplying cells, the subsequent inflammation could lead to fibrosis. In cases of hypospadias repair failure ending in strictures, the urethral tube lacks the support of the spongiosum, resulting in stricture recurrence.

Table 1: Acellular scaffolds used in treating urethral strictures.

Author	Year	Scaffold	Patient age (years)	Stricture length (cm)	Technique	Follow-up (months)	Success rate
Atala et al.[7]	1999	BAMG	4–20	5–15	Patch onlay	22	3/4 (75%)
Mantovani et al.[8]	2002	SIS	-	3–10	Dorsal onlay	6	4/4 (100%)
Mantovani et al.[9]	2003	SIS	72	-	Patch dorsal onlay	16	1/1 (100%)
El-Kassaby et al.[10]	2003	BAMG	22–61	1.5–1.6	Patch ventral onlay	36–48 (mean: 37)	24/28 (86%)
Lin et al.[11]	2005	ADMG	18–46	-	Tubular	12–72 (mean: 45.6)	14/16 (88%)
Le Roux[12]	2005	SIS	15–56	1–4	Tubular, endoscopic urethroplasty	12–24	2/8 (22%)
Donkovic et al.[13]	2006	SIS	26–45	4–6	Patch dorsal onlay	18	8/9 (89%)
Hauser et al.[14]	2006	SIS	61–80	3.5-10	Patch dorsal onlay	3.7–17.5 (mean 12.4)	1/5 (20%)
Palminteri et al.[15]	2007	SIS	20–74	2–8	Patch dorsal inlay, patch ventral onlay, patch dorsal inlay plus ventral onlay	13–35 (mean: 21)	17/20 (85%)
Fiala et al.[16]	2007	SIS	45–73	4–14	Patch ventral onlay	24–36 (mean: 31.2)	40/50 (80%)
El-Kassaby et al.[17]	2008	BAMG	21–59	2–18	Patch onlay	18–36 (mean: 25)	10/15 (67%)
Farahat et al.[18]	2009	SIS	20–52	0.5–2	Patch endoscopic dorsal inlay	12-24 (mean: 14.25)	8/10 (80%)
Palminteri et al.[19]	2012	SIS	23–66	1.5–6	Patch dorsal inlay, patch ventral onlay, patch dorsal inlay plus ventral onlay	52–100 (mean: 71)	19/25 (76%)
Von Seggern et al.[20]	2013	SIS	61*	1–15	Patch onlay	0.4–94.9 (mean: 28.4)	34/49 (69%)
Riberio-Filho et al.[21]	2014	UAMG	10–71	3–18	Ventral onlay	24–113	33/44 (100%)

*mean value.
BAMG: bladder acellular mucosal graft; SIS: small intestine; ADMG: acellular dermal matrix graft; UAMG: urethral acellular matrix graft.

In the past, urologists believed in treating urethral strictures progressively starting from simple procedures moving towards complex treatment options even though repeated unsuccessful attempts at less invasive procedures can make future surgical repair more difficult.[64] Though urethroplasty has a 95% success rate, many urologists have little experience performing this procedure, resulting in their preference for repeated endoscopic procedures in spite of unsatisfactory results.

QUALITY OF LIFE OUTCOMES

The success rates associated with the surgical techniques employed to treat urethral strictures have been well-documented. However, the outcomes relating to the patient's quality of life, including sexual function, are less widely known and reported. Temporary erectile dysfunction following anterior urethroplasty is a known complication and may occur in up to 38% of men, with the highest incidence of erectile dysfunction following bulbar urethroplasty.[65] However, patient ejaculatory function is less well-documented. Validated instruments to define and document patient related outcomes and quality of life are necessary to obtain a good measure of success following reconstructive surgery.

TISSUE ENGINEERED CONSTRUCTS IN URETHRAL RECONSTRUCTION

Tissues currently used for urethroplasty lack the biochemical, mechanical, structural, and/or functional properties of the native urethra and are associated with complications, such as donor site morbidity, rejection, and/or suboptimal performance. However, tissue enginnering has demonstrated promise in developing tissue subtitutes that can restore urethral function in the form of acellular matrices as well as cell-seeded tissue engineered constructs.

A number of acellular extracellular matrix-based scaffolds have been used to treat urethral strictures, as summarised in Table 1.[7-21] The efficacy of the acellular grafts is dependent on the extent of vascularisation of the graft and regeneration of epithelial mucosa by infiltration of epithelial cells from adjacent areas. In patients with severe spongiofibrosis and patients with long strictures, acellular grafts do not perform well due to the lack of vascularity and offer only limited epithelial regeneration.[17,19] Epithelial regeneration has been demonstrated in a maximum length of 0.5 cm, thus limiting acellular graft application.[66]

Table 2: Cell-seeded constructs used in treating urethral strictures.

Author	Year	Cells	Scaffold	Patient age (years)	Stricture length (cm)	Technique	Follow-up (months)	Success rate
Fossum et al.[22]	2007	Autologous UC from bladder washings	ADM	1–3.7	-	Onlay	35–68 (mean: 51.2)	5/6 (83%)
Bhargava et al.[23]	2008	Autologous OEC/OF	ADM	36–66	-	Onlay	32–37 (mean: 33.6)	3/5 (60%)
Raya-Rivera et al.[24]	2011	Autologous BUC/BSMC	PGA/ PLGA	10–14	4–6	Tube	36–76 (mean: 64.2)	4/5 (80%)
Fossum et al.[25]	2012	Autologous UC from bladder washings	Dermis	1–3.7	-	Onlay	72–103 (mean: 86)	5/6 (83%)
Osman et al.[26]	2014	Autologous OEC/OF	ADM	36–66	-	Onlay	110–115 (mean: 112)	3/5 (60%)
Beier et al.[27]	2014	Autologous OEC	Collagen matrix	24–70	4–7	Onlay	3–18 (mean: 9.3)	8/10 (80%)
Ram-Liebig et al.[28]	2015	Autologous OEC	Collagen matrix	24–76	2–8	Onlay	13–22	17/21 (81%)

ADM: acellular dermal matrix; UC: urothelial cells; OEC: oral epithelial cells; OF: oral fibroblast; BUC: bladder urothelial cells; BSMC: bladder smooth muscle cells; PGA: polyglycolic acid; PLGA: polylactic-co-glycolic acid.

Tissue engineered cell-seeded grafts may be ideal for long segment and complex strictures as they may succeed in lengthening the distance over which epithelial regeneration occurs. Despite significant progress in developing novel cell-seeded constructs for urethral substitution and subsequent success in preclinical studies, very few have progressed to clinical studies (Table 2). Five patients with LS strictures underwent urethroplasty with oral epithelial and oral fibroblast seeded de-epidermised dermis.[23] One patient required full graft excision and another required a partial excision due to fibrosis during short-term follow-up. After 9 years, four out of the five patients still have patent and normal urethras.[26]

Six hypospadias patients were treated with acellular dermis scaffolds seeded with urothelial cells obtained from bladder washes.[22] One patient developed a stricture and two developed fistulae which were surgically corrected. However, long-term follow-up showed that four out of six patients in this study had a bell-shaped urine flow rate curve with no evidence of stricture or fistula.[25] Five paediatric patients were treated with bladder derived urothelial cells and smooth muscle cell seeded polyglycolic acid: polylactic-co-glycolic acid scaffolds which were tubular in shape.[24] At a mean follow-up of 71 months, the success rate was 100% with all patients showing the maintenance of patent urethra without strictures. MukoCell® is a commercial tissue engineered collagen matrix seeded with autologous oral epithelial cells available exclusively to patients in Germany. MukoCell was used to treat 10 patients with a success rate of 80% after a mean follow-up of 9.3 months.[27] Strictures reoccurred in two patients within the first 3 months. The success rate of MukoCell in 21 patients was 81% after a mean follow-up of 18 months.[28] All the above studies demonstrate the feasibility and efficacy of using tissue engineering based approaches for the treatment of complex urethral strictures.

There are several challenges associated with developing tissue engineered therapies for urethral reconstruction. A significant challenge is the non-availability of large animal models which mimic the pathophysiology of USD to evaluate the tissue engineered urethral substitutes. These models need to be developed in order to obtain reliable data about the safety and efficacy of novel tissue engineered substitutes. Another challenge lies in the sourcing of cells. Currently, tissue engineered urethral substitutes have primarily focussed on repairing or replacing the epithelial cell layer in the urethral lumen. However, in the case of severe spongiofibrosis, an efficacious urethral substitute must contain epithelial cells in the lumen in conjunction with endothelial cells and corporal smooth muscle cells in order to repair the damaged corpus spongiosum. In such an approach, the donor source for these cell types is a significant challenge. Finally, tissue engineered products are also met with challenges concerning regulatory issues, and high development and manufacturing costs. Tissue engineered products are positioned to enter the market within a landscape of strict legal regulation and guidelines concerning patient safety. Therefore, the onus of adhering to strict rules lies on all scientists and clinicians, which may limit the possibilities of carrying out specific research. For a typical tissue engineering product, a minimal research and development time of 5 years with a concomitant investment of more than €10 million is necessary.[67] In addition to manufacturing (which is currently very expensive) costs include characterisatoin of materials and culture media, and safety and efficacy testing, thereby limiting the development of substitutes.

FUTURE

Urethral stricture has been a complex problem from time immemorial. New technologies and techniques have enabled urologists to provide patients with prolonged periods of non-obstructive urine flow. Tissue engineering, on the other hand, has been able to provide different materials to improve the success rate with decreased morbidity. However, the knowledge of the underlying mechanism of USD remains limited and therefore, USD remains a challenge to conquer for clinicians worldwide.

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RECENT ADVANCES IN THE PHARMACOTHERAPY OF PREMATURE EJACULATION

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ABSTRACT

Premature ejaculation (PE) can be a very distressing condition and has been studied for many years. However, there exists confusion about the definition, incidence, and management of this condition. Treatment through pharmacotherapy has been focussed on topical agents along with oral antidepressant medications. The use of sexual psychology can also play a role in treatment of PE, often when added to medical therapies. Other alternative medical treatments have also been used with mixed outcomes. Although there is no perfect treatment for PE that works for every patient every time, there is ongoing research for the optimal therapy for men who complain about this problem. A review of the current understanding and medical management of PE will be set in this paper along with potential future treatments.

Keywords: Premature ejaculation (PE), ejaculatory dysfunction, pharmacotherapy.

INTRODUCTION

Premature ejaculation (PE) was first described by Gross in 1887[1] and is thought to be one of the most common sexual dysfunctions affecting men today.[2] However, the exact definition, epidemiology, pathophysiology, and management of PE have been disparate over time.[3] The past several years have seen an increasing amount of research on PE, which has continued to change our perception regarding this condition, along with its management.[3,4] Several professional organisations, such as the American Psychiatric Association (APA) and the International Society for Sexual Medicine (ISSM), have updated their definitions of PE to reflect the currently accepted and more evidence-based findings pertaining to PE.[5,6] The newer and more concrete definitions allow for a better understanding and study of PE.

Today, a basic definition of PE is the following: i) an ejaculation that occurs in <1 minute from vaginal penetration (primary or lifelong PE) or <3 minutes (secondary or acquired PE); ii) ejaculation that cannot be postponed in nearly all attempts at vaginal penetration; and iii) personal distress with negative consequences such as avoidance of sexual relations.[6]

Despite our improved understanding of what truly constitutes PE, the optimal management of this condition remains a matter of debate. In the last century, the main treatment has consisted of various psychotherapy options.[7,8] However, discoveries on the central regulation of ejaculation and the therapeutic role of serotonergic agents in PE revolutionised the treatment of this condition.[9] This article aims to summarise the pathophysiology of PE and discuss its current medical treatment alternatives in the light of the most recent publications. We have conducted a search of the PE pharmacotherapy literature using the PubMed and Medline databases in January 2017, limited to original research publishedin English. Reference lists of identified articles were also reviewed for relevant publications.

PATHOPHYSIOLOGY OF PREMATURE EJACULATION

Ejaculation is thought to be controlled by many different physical pathways. The spinal ejaculatory generator (SEG),[10] neuroendocrine issues,[9,11] along with comorbid urological conditions[12-14] can all affect ejaculation. The SEG works in concert with

parasympathetic, sympathetic, and motor output in emission and expulsion phases of ejaculation.[10,15] When certain thresholds of stimulation are met on the visceral, proprioceptive, and somatosensory neuronal input to the SEG and supraspinal sites, activation or inhibition of ejaculation occurs.[15]

Although we understand how ejaculation occurs, we still do not fully know the mechanisms that contribute to the pathology of PE. It has been theorised that hyposensitivity of the 5-HT2C or hypersensitivity of the 5-HT1A receptors could be the cause of lifelong PE.[16] The same authors proposed that men with low serotonin may have a lower ejaculatory set-point resulting in PE. This theory would also help to explain delayed ejaculation in those with a genetically higher set-point.[17] Hormones are known to play a role in ejaculation and timing, such as dopamine, oxytocin, testosterone, and prolactin.[18,19] Additionally, comorbid urologic conditions like prostatitis can be associated with PE.[12,20] Varicoceles have also been thought to contribute to pelvic venous congestion and symptomatic prostatitis resulting in PE,[21] wherein after surgical correction of the varicocele, symptoms of PE were improved.[13] Certainly the myriad of biological causes of PE are not well elucidated, but we are gaining a better understanding of the condition which may help guide future treatment options.

The contribution of the psychological factors to the biological ones makes the pathophysiology of PE even more complex. Psychologically, men with PE have high rates of dissatisfaction with sexual intimacy and relationships.[22-24] The partners of men with PE were studied using a validated sexual questionnaire, which reported that the female partners were also negatively affected with decreased sexual satisfaction when they had sex with a man who has PE.[25,26] One theory suggested that men with PE had increased sympathetic activities due to anxiety which promotes smooth-muscle contraction resulting in PE.[27] There is some psychopathology associated with PE in the form of decreased self-esteem and self-confidence, increased interpersonal problems, mental obsession with ejaculation and performance, and increased embarrassment/shame/guilt/worry about sexual failure and the inability to please the partner.[23,24] Therapies directed at treatment of these comorbid conditions, which may be the result or the cause of PE, are important prescriptions in the healing from PE.

PSYCHOTHERAPY FOR PREMATURE EJACULATION

The first treatment modalities for PE were with psychotherapy focussing on the sexual relationship and anxiety related to sexual satisfaction with a partner.[28,29] A behaviour modification technique was popularised by Master and Johnson[30] as they described the 'squeeze' and later 'start-stop' method. This is a form of sensory behavioural therapy, which is thought to train the mind and body around ejaculatory timing, psychological excitation, and stimulation responses.[31] However, these types of techniques have not reliably been able to increase the intravaginal ejaculatory latency time (IELT).[28,31,32]

Psychotherapies directed at increasing sexual knowledge, relationship strengthening, interpersonal resolution of sexually related disorders, treatment of psychopathologies that may lead or result in PE, increasing sexual skills set, and reduction of performance anxiety, have been suggested as helpful treatment regimens for PE.[33,34] However, many psychological studies are not strongly evidence-based and have methodological flaws and are hence considered to be adjuvant treatments along with pharmacotherapy.[33,35] In two meta-analyses published more recently, it was shown that the intervention with psychotherapy was inconsistent, which means more research is needed to assess efficacy.[36,37] Until more quality research is produced, it is advised to use psychotherapy in combination with pharmacotherapy for treatment of PE.

PHARMACOTHERAPY FOR PREMATURE EJACULATION

Topical Anaesthetics

In 1943, the first medical treatment for PE was suggested by Schapiro.[29] He described how topical anaesthetics may help to delay ejaculation by decreasing the hypersensitivity of the glans penis during sexual intercourse as hypersensitivity of the glans is one of the proposed aetiological factors in the pathophysiology of PE.[38]

The basic topical medications used to treat PE tend to be lidocaine based.[39] A trial of 5% lidocaine-prilocaine cream increased the IELT when it was applied 20 minutes prior to sex in a randomised, placebo-controlled double-blind trial.[40] A study that looked at a combination of lidocaine-prilocaine cream versus a phosphodiesterase Type 5 inhibitor (PDE5-I) showed that the topical agent worked

much better in patient satisfaction rates and IELT times for PE.[41] Administration changes of topical agents have showed success with IELT in PE. There is a topical spray mixture for PE known as TEMPE Spray (Plethora Solutions Ltd, London, UK) that contains lidocaine-prilocaine which increased IELT by 6.3-times compared to baseline with excellent patient satisfaction and reported outcomes.[42] There have also been more natural products that have had good outcomes in terms of success in topical application for treatment of PE. One of these is known as Severance-Secret (SS)-cream and is a mixture of nine herbal supplements.[39] One study of SS-cream demonstrated an increase of baseline IELT from 1.37 to 10.92 minutes with reported sexual satisfaction rates of 82% in a controlled study.[43] However, with every treatment comes some adverse effects. With the topical anaesthetics, there have been reports of hypoaesthesia in the partner, thought to be from direct transfer of the topical agent to the vagina. If a condom is not used, this transfer can result in vaginal anaesthesia and anorgasmia in the female.[44]

Selective Serotonin Reuptake Inhibitors

When the regulation of serotonin is disrupted in the central nervous system, ejaculation can be altered, resulting in one of the proposed aetiologies of PE.[45,46] From studies in animals and humans, it has been determined that the serotonin neurotransmitter has the greatest impact on ejaculation and timing.[16,47] Because of these findings, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and selective norepinephrine, and serotonin reuptake inhibitors have all been used in the management of PE.[48] These drugs prevent the reabsorption of serotonin from the axonal end within the synaptic cleft. This results in an increase in serotonin within the microneuronal environment and increased serotonin stimulation in the post-synaptic receptors. Increasing serotonin levels then results in a delay of ejaculation. Dapoxetine is a fast-acting SSRI that can be used to treat PE on demand and it is often considered as the first-line drug therapy.[49] With the recently developed delivery methods, dapoxetine appears to have an even quicker onset of action and bioavailability from sublingual and intranasal routes.[50] Dapoxetine is not approved for use in the USA and paroxetine has been used on an on-demand basis or daily as it has a relatively greater efficacy in delaying ejaculation.[51,52] Other SSRIs would need to be used daily (paroxetine, clomipramine, sertraline, fluoxetine, or citalopram) (Table 1).[46,53-60]

The doses of SSRIs that are effective in increasing IELT are paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, and citalopram 20–40 mg (Table 1).[53-55,58,60,61] It has been shown that paroxetine has been the most effective with an 8.8-fold increase in IELT compared to the other SSRIs.[62] Generally, it takes time for these drugs to assert their effect. However, some may seem to affect ejaculation within 5–19 days, with the maximal effect usually being reached within 2–3 weeks of daily treatment.[63] The side effects of SSRI treatments are relatively minor and may even dissipate after 2–3 weeks of continued use.[64] The most common side effects are mild nausea, diarrhoea, yawning, constipation, insomnia, and fatigue.[64] Some degree of sexual dysfunction in the form of erectile dysfunction, low libido, or hypoactive desire was reported with SSRI use for PE.[65] Additionally, patients who are interested in fertility should use SSRIs with caution as there has been evidence of decreased sperm parameters with SSRI use.[66]

Perhaps the most serious side effect of SSRI use is the suicide risk which may occur in the early phase of the treatment for young adults, adolescents, and children with concurrent psychiatric disorders.[67] Suicidal thoughts should be appropriately screened with a low-threshold for referral to psychiatric care if needed. In adult men with PE, such risk was not very significant, but clinicians should still exercise caution when prescribing such medications.[51,59]

When evaluating the compliance of SSRIs for patients being treated for PE, there seems to be a 30% incidence of non-starters for paroxetine (10 mg daily for 21 days followed by 20 mg as needed) and another 30% who did not follow-through with treatment after they had started, citing that the side effects of treatments seemed to be worse than the PE condition (treatment less effective than expected, fear of being on an antidepressant, loss of interest in sex from relationship, or drug side effects).[68] There have not been a lot of side effects from the use of dapoxetine on demand dose, but those that were reported included headaches, dizziness, and nausea, and were dose-dependent.[59,69] Although the majority of lifelong PE patients prefer daily drug treatment,[70] some men may be willing to use on-demand dapoxetine because of the potential side effects of continuous SSRI use. However, it has been shown that about 20% of men do not want to be on any drug due to fear of side effects or cost and hence never start treatment with dapoxetine.[71]

Table 1: Medical treatment options for premature ejaculation.[97]

Drug (Trade name)	Dose	IELT fold increase	Timing	Common side effects
Oral therapy SSRIs				
Dapoxetine (Priligy®)[59]	30–60 mg on demand	2.5–3	PRN, FA	Nausea, diarrhoea, headache, dizziness, somnolence, decreased sexual desire
Clomipramine (Anafranil®)[53,62]	12.5–50 mg/day or 12.5–50 mg on demand	6 4	PRN	
Fluoxetine (Prozac®, Sarafem®)[61]	20–40 mg/day	5		
Paroxetine (Paxil®, Seroxat®)[62,98]	10–40 mg/day or 10–40 mg/day on demand	8 1.4	PRN	
Sertraline (Zoloft®)[58]	50–200 mg/day	5		
Citalopram (Celexa®, Cipramil®)[54]	20–40 mg/day	2		
Tramadol (Zertane®)[75]	62 mg ODT on demand or 89 mg ODT on demand	2.4 2.5	PRN	In addition to above: Addictive, respiratory depression, serotonin syndrome, dyspepsia, constipation
Topical therapy				
Lidocaine/prilocaine cream (EMLA®)[44]	25 mg/gm lidocaine, 25 mg/gm prilocaine	4–6	PRN, FA	Penile numbness, partner genital numbness, local erythema

SSRI: selective serotonin reuptake inhibitors; IELT: intravaginal ejaculatory latency time; PRN: as needed; FA: fast acting (quick on-set of action); ODT: orally dissolving tablet.

In fact, 90% discontinued dapoxetine within a year for a number of reported reasons: expected outcome less than hoped for (24.4%), price of the drug (24.4%), decreased libido or sex drive felt to be from the drug (19.8%), and the drug not being effective to treat the condition (13.9%).[71]

Tramadol

Another drug that has been used to help with PE is tramadol. This drug can be used as needed or daily to help with PE by increasing the IELT.[72] The mechanism of action of tramadol is to bind the μ-opioid receptors and weakly inhibit the serotonin/norepinephrine reuptake receptors, which results in analgesia.[73] Tramadol in doses of 25–100 mg has been shown to increase the IELT by 2.4 to 12.6-fold in controlled clinical trials.[74,75] Unfortunately, as effective as tramadol can be, it can also have severe negative consequences including drug addiction, somnolence, pruritus, dizziness, dry mouth, vomiting, and nausea, which can all be dose-dependent.[74,75] Additionally, the combination of tramadol with an SSRI can be fatal due to induction of a serotonin syndrome and should therefore be avoided.[76]

Phosphodiesterase Type 5 Inhibitors

PDE5-Is have been well-studied and may marginally help those who have comorbid erectile dysfunction and PE.[77] Some men have conditioned themselves to have a more rapid ejaculation due to the inability to maintain erections and for this population it is proposed that PDE5-Is may be helpful to prolong the sexual experience, but there is no robust evidence that have supported the use of PDE5-Is in PE patients who do not have concomitant erectile dysfunction.

Other Drugs and Treatments

Oxytocin and dopamine are two neurochemicals that effect ejaculation and which have been used for some therapeutic benefit in ejaculatory dysfunction.[11,78] Oxytocin has been shown to shorten ejaculatory latency periods and decrease the refractory period as well in both animals and humans.[79,80] Studies have also been done on rats, which demonstrated that an oxytocin antagonist resulted in delayed ejaculation.[81,82] One promising trial used an oxytocin antagonist to help prolong ejaculation while acting on peripheral and central oxytocin receptors.[78] Further clinical studies are needed to support oxytocin manipulation treatments for PE.

Alpha-1 adrenoreceptors seem to play role in the ejaculation process[83] and inhibiting their function with alpha blockers (silodosin, tamsulosin hydrochloride, alfuzosin, terazosin, and doxazosin) is hypothesised to be an effective treatment for PE.[84]

Among these drugs, silodosin is associated with higher risk of abnormal ejaculation,[85-87] as 14% of subjects treated with silodosin reported a reduction or absence of ejaculation compared to tamsulosin (2.1%) and placebo (1.1%).[88] Sato et al.[89] evaluated the feasibility of off-label silodosin (4 mg) treatment in eight patients with PE and demonstrated that this drug has an ejaculation-delaying effect (from 3.4 to 10.1 minutes, p=0.003) when it is taken 2 hours before the planned sexual intercourse. These results support the possible use of α1-adrenoceptor antagonists as a new treatment option for PE; however, further placebo-controlled trials assessing this application are needed.

Botulinum neurotoxin, which is produced by *Clostridium botulinum,* is a highly potent biomolecule which prevents the release of the acetylcholine from the neuronal endings at the neuromuscular junction and causes flaccid paralysis.[90] It has been hypothesised that paralysing the muscles which are involved in the ejaculation process (i.e. bulbospongiosus and ischiocavernosus muscles) may delay ejaculation latency, thus ameliorating the PE condition.[91] It was also recently demonstrated that botulinum-toxin injection into the bulbospongiosus muscle in rats was associated with an increase in the ejaculatory latency without affecting the ability to achieve erection or ejaculation.[92] However, clinical studies to demonstrate the efficacy and safety of this treatment modality in men with PE are warranted.

Modafinil is an oral wakefulness-promoting drug that is mainly used for the treatment of narcolepsy.[93] It exerts this effect by interacting with norepinephrine, serotonin, dopamine, and GABA-containing neuronal systems. In addition to its stimulant effect on wakefulness, it has been demonstrated that it can increase the ejaculation latency in rats without suppressing sexual behaviour.[94] This effect has been confirmed in a case study of a lifelong PE patient,[95] whereas Tuken et al.[96] demonstrated that on-demand modafinil treatment significantly increased mean IELT and improved patient reported outcomes in 55 lifelong PE patients. Future controlled clinical trials are necessary to confirm these findings.

CONCLUSION

Pharmacotherapy for PE tends to be 2-fold: topical application of anesthetic agents and daily or on-demand SSRIs. All pharmacologic agents have some side effects, which can affect patient compliance to treatment. Tramadol and PDE5-Is have some therapeutic effect but much less than the proven therapies. *C. botulinum* toxin and modafinil are promising pharmacologic agents for PE treatment, but their efficacy must be confirmed in well-designed clinical trials. The future of PE pharmacotherapy is beginning to flourish with research. Ideas on drug delivery, understanding of ejaculatory physiology and hormones, as well as uses of various pharmacologic agents are paving the way for promising future PE treatments.

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RENAL STONES: A CLINICAL REVIEW

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ABSTRACT

Renal stones are a common condition causing significant morbidity and economic burden. The prevalence of urinary tract stones in the developed nations ranges from 4–20%. Renal stones are of different types, the most common being the calcium oxalate stones. Various dietary, non-dietary, and urinary risk factors contribute to their formation. Their frequent association with systemic diseases (like hypertension, diabetes, and obesity) highlights the role of dietary and lifestyle changes in their occurrence, recurrence, and possible prevention. Non-contrast computed tomography (CT) identifies almost every stone and is the preferred investigation for identification. Ultrasound has its advantages, as it is low cost and requires no radiation, but is observer dependent. Metabolic profiles (including blood calcium, phosphate, magnesium, creatinine, uric acid, sodium, and potassium) should be measured and a detailed urinalysis should be done. This review further discusses the formation in depth, and covers risk factors and management of renal stones, and lays down the importance of preventive measures to avoid their recurrence.

Keywords: Renal stones, nephrolithiasis.

INTRODUCTION

Renal stones, or nephrolithiasis, are a common problem worldwide. With its increasing prevalence, they are imposing a significant economic burden for both developing and developed nations. It has been observed that renal stones are associated with systemic diseases like Type 2 diabetes mellitus, obesity, dyslipidaemia, and hypertension. Lifestyle and environmental factors contribute significantly in their formation. Presentation of renal colic is common and therefore treatment is not delayed. However, in the absence of any preventive measures >50% of renal stones may reoccur. This review summarises the pathophysiology of renal stones and discusses the clinical management for prevention and treatment of renal stones.

EPIDEMIOLOGY

Renal stones can occur at any age; the peak incidence is reported in persons aged 20–49 years. Males are affected more than females. The prevalence of urinary tract stones in the industrialised world ranges from 4–20%.[1,2] In Italy prevalence of urinary tract stones was found to be 1.2%, in Scotland 3.5%, and in Spain 10.0%.[3,4] They are rare in Greenland and coastal areas of Japan. In USA, the prevalence of nephrolithiasis was 10.6% in men and 7.1% in women. On average, 1 in 11 Americans develop kidney stones at least once in their lifetime.[1,5] In developing countries, bladder calculi are more common than upper urinary tract calculi; the opposite is true in developed countries. It is estimated that the incidence of renal stones may increase from 40% to 56% by 2050 as a result of the effects of global warming.[5]

Table 1: Different types of renal stones

Composition	Frequency
Calcium oxalate	75%
Calcium phosphate	15%
Uric acid	8%
Struvite	1%
Cystine	<1%

Table 2: Factors causing increased risk of renal stones.

Factor	Example
Metabolic	High urine calcium
	High urine oxalate
	Low urine citrate
	Low urine volume
Dietary	Low fluid intake
	Low calcium intake
	High intake of animal protein
	High oxalate intake
Infections	Recurrent urinary tract infection
Hereditary	Positive family history
Congenital anatomic defects	Medullary sponge kidney, horseshoe kidney, and ureteropelvic junction obstruction
Environmental	Hot and arid climate. People working outdoors in hot weather have an increased risk of stone formation due to excessive fluid loss from sweating.
Systemic disorders	Hyperparathyroidism, diabetes mellitus, hyperuricemia, metabolic syndrome etc.

Renal stones are common in obese and diabetic individuals. The recurrence rate of renal stones is high, with 50% recurring within 5 years of the initial stone event. The factors that determine the accelerating pace of stone formation in recurrent stone formers are not well known. Therefore, in any single stone former, one cannot predict which patient will relapse, however, the natural history of stone disease and the high rate of recurrence requires careful diagnostic evaluation and early treatment.

CLASSIFICATION OF RENAL STONES

There are different kinds of renal stones and their correct identification is important in the selection of optimal treatment. The frequency of different stone type occurrence is shown in Table 1.[6]

There are various risk factors for the development of stones in the urinary tract, for example dietary, non-dietary, and urinary. These risk factors vary by stone type and by clinical characteristics.[7,8] Major factors causing an increased risk for the development of renal stones are mentioned in Table 2.

PATHOPHYSIOLOGY

Renal stones are composed of insoluble salts from the urine and are formed by two basic mechanisms. The first mechanism is the aggregation of crystals with a non-crystalline protein (matrix) component. The salts in the urine precipitate and crystallise, aggregating the crystals, and causing them to grow into a mass sufficient to cause clinical symptoms.[6] In the second mechanism, which is mostly responsible for calcium oxalate stones, deposition of stone material occurs on a renal papillary calcium phosphate nidus, typically a Randall's plaque (which always consists of calcium phosphate).[7] The majority of stones are composed of mostly calcium salts, including those of calcium oxalate and calcium phosphate. Uric acid, cystine, and magnesium ammonium phosphate (struvite) compose the remainder of the stones.

CLINICAL MANIFESTATIONS

The three narrowest parts of the ureter are at the pelvo-ureteric junction, the mid-ureter, where the ureter crosses the iliac vessels, and the vesico-ureteric junction (VUJ). The VUJ is the most common site of obstruction. Patients may present with renal colic, experiencing a severe sharp pain at the flanks which has a sudden onset, with fluctuation and intensification over 15–45 minutes. It then becomes steady and unbearable, often accompanied by nausea and emesis. As the stone passes down the ureter towards the bladder, flank pain changes in a downward direction towards the groin. When the stone is lodged at the VUJ, urinary frequency and dysuria may appear. The pain may clear as the stone moves into the bladder or from the calyceal system into the ureter. Stones may obstruct the urinary tract and impair renal function. There is an increased risk of infection with

chronic obstruction. Bleeding may be chronic and accompany obstruction. The presence of bleeding alone does not predict a more severe outcome. Episodes of rapid onsets of pain, bleeding, and then rapid clearing, often known as 'passing gravel', are the result of passing a large amount of crystals of calcium oxalate, uric acid, or cystine. Some patients experience painless haematuria.[9,10] The close differential diagnoses, which should be excluded before diagnosing renal colic, are abdominal aortic aneurysm, appendicitis, bowel obstruction, cholecystitis, mesenteric ischaemia, musculoskeletal pain, ovarian abscess, ruptured ovarian cyst, pelvic inflammatory disease, and pyelonephritis.[11,12]

EVALUATION OF STONE FORMERS

A detailed history and examination is required to evaluate renal stones. History of gout and recurrent urinary tract infection (UTI) should specifically be asked as hyperuricaemia in patients with gout can precipitate uric acid stones, whereas UTI can predispose the patient to struvite stones. Fasting blood calcium, phosphate, magnesium, creatinine, uric acid, sodium, and potassium should be measured.[12] A detailed urinalysis should be conducted, which includes measurement of pH, albumin, glucose, 24-hour urine calcium, phosphate, magnesium, creatinine, oxalate, uric acid, citrate, and cystine.[13]

Imaging

All patients suspected of harbouring a stone in the urinary tract should undergo an imaging procedure to determine whether the new stone is located within the kidney parenchyma, renal pelvis, upper or lower ureter, or bladder, and whether there is ureteral obstruction.[14] The localisation of stones is also important in choosing medications, surgery, or lithotripsy. Ultrasonography (USG) is used frequently to determine the presence of a renal stone. Uric acid or cystine stones are easily identifiable on USG but are not visible on plain radiograph. An advantage of USG is that it is easily available, does not require any intravenous (i.v.) contrast, and can detect hydronephrosis easily. The success of USG is dependent on the operator's skill and experience.[15] Ultrasound may not accurately visualise all stones and therefore cannot be used for follow-up to determine the appearance of new stones. Non-contrast computed tomography (CT) of the abdomen with 5 mm cuts is the most sensitive imaging technique for determining the number and location of stones within the renal parenchyma or along the upper or lower urinary tract. Using this technique, stones can be distinguished from kidney tissue or blood clots. Nephrocalcinosis can be identified as a myriad of tiny, almost microscopic, specks of radiodense calcium arrayed along the calyces. Small, separate, radiodense stones of <1 cm in diameter suggest calcium, or less commonly, cystine stones. Radiodense stones suggest either calcium or struvite composition, but struvite stones are usually large and fill the calyceal system. Cystine stones appear to be radiodense, but less dense than calcium containing stones. Small, radiolucent stones suggest uric acid composition. Uric acid stones appear as filling defects on i.v. pyelography. Filling defects that occupy the renal pelvis are staghorn stones and may be of struvite, uric acid, or cystine composition. Sludge may be of either uric acid or cystine, which can fill the renal pelvis and cause obstruction. Plain radiographs of the abdomen can identify large radiopaque stones of ≥3 mm.[16]

MANAGEMENT

Management of Acute Colic

Treatment of renal colic in the emergency setup involves i.v. fluids, analgesics and anti-emetic medication, and anti-emetic medication. When the diagnosis of renal colic is established, presence of obstruction or infection should be determined. In 2016, the American Urological Association (AUA) and the Endourological Society issued general management guidelines for the various presentations of stones that can be managed conservatively. The guidelines state that observation, with or without medical expulsive therapy, should be offered to patients with uncomplicated distal ureteral stones that are ≤10 mm in diameter. The guidelines also state that active surveillance can be offered for asymptomatic, non-obstructing calyceal stones. Urological intervention should be sought if there is evidence of UTI, a stone >8 mm in diameter, any anatomic abnormality, or intractable pain.[17,18]

Prevention of New Stone Formation

Without medical treatment, the 5-year recurrence rate is high, ranging from 35–50% after an initial stone event. A high fluid intake, enough to produce at least 2.5 L of urine per day, should be the initial therapy to prevent stone recurrence.[19] Recommendations for preventing stone formation depend on the stone type and the results of metabolic evaluation. After remediable secondary causes of stone formation

(e.g. primary hyperparathyroidism) are excluded, the focus should turn to modification of the urine composition to reduce the risk of new stone formation. Dietary modifications have a major role in the management of recurrent stones that are due to hypercalciuria. Dietary calcium should not be restricted, since calcium reduces the excretion of urinary oxalate by decreasing intestinal absorption of oxalate. Guidelines from the AUA recommend a daily calcium intake of 1,000–1,200 mg. Moreover, restriction of dietary calcium to <800 mg/day (the current recommended daily allowance for adults) can lead to negative calcium balance and bone loss. Sodium intake also influences hypercalciuria. Calcium is reabsorbed passively in the proximal tubule due to the concentration gradient created by active reabsorption of sodium. A high sodium intake causes volume expansion, leading to a decrease in proximal sodium and calcium reabsorption and enhancing calcium excretion. A low-sodium diet (80–100 mmoL/day, or 1,800–2,300 mg/day) is recommended.[20] This enhances proximal sodium and passive calcium absorption and leads to a decrease in calcium excretion. Dietary protein increases the acid load by production of sulphuric acid and leads to hypercalciuria by its action on bone and kidney. Animal protein has a higher content of sulphur and generates a higher acid load compared to vegetable protein, with animal protein associated with an increased incidence of stone formation. It has been seen that the combination of restricted intake of animal protein (52 g/day), restricted salt intake (50 mmoL, or 2,900 mg/day of sodium chloride), and normal calcium intake (30 mmoL/day, or 1,200 mg/day) was associated with a lower incidence of stone recurrence in men with hypercalciuria, compared with traditional low-calcium intake (10 mmoL, or 400 mg/day). Patients should therefore be advised to avoid excessive intake of animal protein.[21]

Specific Recommendations for Different Types of Stones[22-24]

Calcium oxalate stones

A reduction in urine oxalate reduces the super-saturation of calcium oxalate. In patients with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production. Firstly, foods that contain high amounts of oxalate should be avoided e.g. spinach, rhubarb, and potatoes. The absorption of oxalate is reduced by higher calcium intake; therefore, individuals with higher than desired urinary oxalate should be counselled to consume adequate calcium. Citrate is a natural inhibitor of calcium oxalate and calcium phosphate stones. More consumption of foods that are rich in alkali (i.e. fruits and vegetables) should be encouraged.

Calcium phosphate stones

Calcium phosphate stones share the same risk factors as with calcium oxalate stones like higher concentrations of urine calcium and lower concentrations of urine citrate. There are no current randomised trials to base preventive recommendations for calcium phosphate stone formers, so the interventions are focussed on modification of the recognised risk factors. Reduction of dietary phosphate may be beneficial by reducing urine phosphate excretion.

Uric acid stones

The mainstay of prevention of uric acid stone formation entails increasing urine pH. While acidifying the urine can be challenging, alkalinising the urine can be readily achieved by increasing the intake of foods rich in alkali (e.g. fruits and vegetables) and reducing the intake of foods that produce acid (e.g. animal flesh). Supplementation with bicarbonate or citrate salts (preferably potassium citrate) can be used to reach the recommended pH goal of 6–7 throughout the day and night.

Struvite stones

These stones require complete removal by a urologist. New stone formation can be avoided by the prevention of UTIs.

Pharmacological Intervention

- For calcium oxalate and calcium phosphate stones thiazide diuretics (with sodium restriction) may be used to reduce urine calcium[25]
- In patients with low urine citrate levels, alkali supplements (e.g. potassium citrate) may be used to increase these concentrations. However, the urine pH of these patients should be monitored carefully because supplemental alkali can raise urine pH, thereby potentially increasing the risk of stone formation
- Calcium channel blockers along with prednisolone have been found to facilitate ureteral stone passage and can be used in patients harbouring stones in the ureter[26,27]
- Tamsulosin, an alpha-1 selective blocker, is usually indicated for the treatment of lower urinary

tract symptoms due to prostatic enlargement. It has also shown positive results in facilitating passage of ureteral stones[27-29]

- Long-term dietary cystine restriction is not feasible and is unlikely to be successful; hence for the prevention of cystine stones, treatment is done with medication that covalently binds to cystine (tiopronin and penicillamine) and a medication that raises urine pH[30]

Surgical treatment

Usually, stones ≤4 mm in diameter pass spontaneously and stones >8 mm are unlikely to pass without surgical intervention. Primary indications for surgical intervention according to AUA guidelines are given in Table 3.

According to the 2005 AUA and 2016 AUA/ Endourological Society guidelines:[18]

1. Ureteroscopy (URS) is considered the first-line therapy for mid distal ureteral stone
2. Percutaneous nephrolithotomy (PCNL) as the cornerstone of management for staghorn calculi
3. Extracorporeal shockwave lithotripsy (ESWL)/ URS for non-lower pole stones with a total stone burden <20 mm or lower pole renal stone <10 mm

PCNL was developed to reduce the morbidity and mortality associated with open renal surgery, and it currently remains the first-line treatment for large renal stones. However, it represents the most morbid of the minimally invasive endoscopic surgeries for renal stones. Amongst the minimally invasive techniques the main options are ESWL and URS.[31] ESWL is usually an outpatient procedure performed with analgesia or sedation.

Table 3: Indications for surgical intervention.

Ureteral stones >10 mm.	Symptomatic renal stones in patients without any other aetiology for pain.
Uncomplicated distal stones <10 mm that have not passed after 4–6 weeks of observation.	Pregnant patients with ureteral or renal stone in whom observation has failed.

A shockwave is generated and focussed on the stone. Both procedures have high success rates for all ureteric stones. The use of ESWL has increased but still PCNL has many advantages over ESWL and in some cases, URS.[32] Recent advancement in minimally invasive surgery involves the novel dual wave handheld lithotripter, which is useful for bladder calculi. Stonebreaker pneumatic lithotripter is more effective for staghorn calculi.[33]

CONCLUSION

The increasing incidence of renal stones is adding to the morbidity and huge economic losses worldwide of this pathology. The technological advances have helped with early diagnosis and treatment. However frequent association of renal stones with metabolic diseases like hypertension, diabetes, and obesity emphasise the importance of dietary practices in their occurrence and reoccurrence. High fluid intake and adopting healthy lifestyle measures are some of the cost-effective measures of preventing renal stones.

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