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"Urology is a large and constantly-evolving field, bringing together experts from across the therapeutic spectrum in the hope of developing effective and patient-tailored treatments."

Spencer Gore, CEO

+ FEATURE

+ ARTICLES

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Aims and Scope

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

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

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

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

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

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EMJ is supported by various levels of expertise:

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

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On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review.

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All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

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We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

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Staff members attend medical congresses as reporters when required.

This Publication

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Front cover and contents photograph: Barcelona, Spain, home of EAU 2019. © Brian Kinney / 123rf.com

EMJ Urol. 7.1

EMJ Innovations 3.1

View some of the latest advances and innovations from across the medical sphere and details their implications for treatment, education, and research.

VIEW JOURNAL ←

Welcome

It is my pleasure to welcome you, on behalf of the whole team here at EMJ, to the seventh edition of *EMJ Urology.* Urological conditions can impact patients' lives in so many different ways, having implications both physical and psychological; it is thus more important than ever for the scientific community to share resources and knowledge to tackle these serious morbidities directly with a determined and collaborative approach. We are delighted to play our part through this year's publication, bringing to light topics from the forefront of this ever-changing field.

We were once again in attendance at this year's European Association of Urology (EAU) congress, this time being held against the backdrop of Barcelona, Spain. Considering the wealth of engaging presentations and overall culmination of experts in the field, we were spoilt for choice regarding networking opportunities with key figures in the field and potential content for this year's edition. More than 10,000 participants were able to share knowledge and insight across a multitude of urological topics, including endourology, prostate cancer, and robot-assisted laparoscopy, truly fostering an environment that embodied one of the central themes of the congress: collaboration. This was particularly evident from the participation of urological bodies and societies outside of Europe, including from New Zealand, China, and the Republic of Korea. Additionally, we witnessed some fantastic abstract presentations; a number of presenters have provided written summaries of their presentations, which can be read in the Abstract Reviews section. If you missed out on any of the excitement, you can find a detailed congress review within these pages.

Throughout *EMJ Urology 7.1*, you'll find a varied and compelling selection of peer-reviewed articles that discuss topics we believe deserve attention. These include a systematic review of scrotal squamous cell carcinoma, an in-depth analysis on the efficacy and safety of flexible ureterorenoscopy for the treatment of large kidney stones, and a discussion on whether the surgical treatment of hypospadias is cosmetic or reconstructive. We also have the pleasure of publishing a novel case study on physiotherapy for post neobladder voiding dysfunction in the treatment of malignant neoplasm, an engaging read that is assured to be of interest to experts both within and outside of the urological field. These manuscripts are in addition to several engaging special features that we feel confident will spark inspired conversations on their respective topics.

Urology is a large and constantly evolving field, bringing together experts from across the therapeutic spectrum in the hope of developing effective and patient-tailored treatments. We are always on the look out for future collaborators, so if you have been inspired by any of the articles or abstracts in this edition of *EMJ Urology*, or indeed in any of our publications, we would love to hear from you. Happy reading!

Spencer Gore

Chief Executive Officer, European Medical Group

View the Latest Advances

in prostate cancer research

APEX is an educational and scientific platform that brings you the latest advances in prostate cancer treatment and cutting-edge advances in technology:

- Webinars, interviews and live Q&As with globally recognised prostate cancer experts
- Webcasts and insights from key congresses and updates to guidelines

These resources provide an up-to-date source of prostate cancer information, current research and expert opinion.

APEX

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UK healthcare professionals are not able to register for this site.

APEX is a Sandoz educational website for healthcare professionals involved in the treatment of men with prostate cancer. The resources have been developed by the speakers, who are solely responsible for the content. These materials are not intended for UK-based healthcare professionals. Medical writing support is provided by Spirit Medical Communications Ltd funded by Sandoz International GmbH.

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Foreword

Dear colleagues and friends,

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

In this issue, we have a wide variety of very interesting papers, including a systematic review of scrotal squamous cell carcinoma, physiotherapy in post neobladder voiding dysfunction in the treatment of malignant neoplasm, a review of the literature regarding the efficacy and safety of flexible ureterorenoscopy in treatment of kidney stones >2 cm, the evaluation and management of interstitial cystitis/bladder pain syndrome, a review of penile fracture, and an answer to the question of whether repair of distal hypospadias is cosmetic or reconstructive.

"In this issue, you will also have the chance to read information about the EAU Congress..."

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 subspeciality. The latest developments are presented and discussed. In this issue, you will also have the chance to read information about the EAU Congress that was held on 15th–19th March 2019 in Barcelona, Spain, 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 A. Erdem Canda

Koç University, İstanbul, Turkey

Congress Review

Review of the European Association of Urology (EAU) 34th Annual Meeting 2019

Location: Fira Gran Via – Barcelona, Spain

Date: 15th–19th March 2019

Citation: EMJ Urol. 2019;7[1]:10-21. Congress Review.

The coastline of Barcelona is dominated by Montjuïc. Take the time to complete the walk up her slopes and you are rewarded with stunning views across the jewel of Catalonia. Looking out to the north, the gothic quarter of Barcelona and Gaudi's masterpiece la Sagrada Familia capture the eye, with Tibidabo visible in the distance. Turning 180º, the Barcelona Olympic Park can be seen and beyond the site of the 1992 Olympic games, the Fira Gran Via congress centre, home to the 2019 European Association of Urology (EAU) Annual Congress.

The EAU 2019 opening ceremony was a rousing affair. As the auditorium filled, and delegates discussed what the next 5 days would hold, the anticipation was palpable. The wait was ended as artistes arrived on stage and performed Bizet's 'Habanera', from his famous opera 'Carmen.' This was followed by the stirring 'Prelude' overture, which was a very fitting piece as soon after the EAU Secretary General, and one of EMJ Urology's own Editorial Board members, Prof Christopher Chapple took to the stage and welcomed the delegates to the 34th EAU Annual Congress. Prof Chapple promoted the EAU Nurses Meeting, which ran in parallel with EAU 2019, highlighting the desire for greater nursing involvement in urological care and the subsequent improvement of practice. Prof Chapple then began the ceremony proper with the award of several prestigious prizes and accolades, including the EAU Willy Gregoir Medal for significant contributions to the development of the urological speciality in Europe to Prof Freddie Hamdy, and the EAU Crystal Matula Award presented to Dr Maarten Albersen. The ceremony then closed with the presentation of the EAU Prostate Cancer Award to Dr Veeru Kasivisvanathan, before the music of Carmen flooded the congress centre once again.

More than 10,000 participants attended the 2019 EAU Annual Congress, cementing the association's meeting as the leading urology event in Europe and a key date

in everyone's diary. Furthermore, EAU 2019 was a record breaker with >5,500 abstracts submitted, providing delegates with an insight into the bleeding-edge of urological research. A total of 88 poster sessions spanning the broad spectrum of fascinating urological research from endourology and spinal surgery, presented on Friday 15th March, to survivorship in prostate cancer and ablative surgery in benign prostatic obstruction relief, on Monday 18th March, was on display. Alongside these, EAU 2019 offered 300 scientific sessions led by >1,500 world leading experts overseeing the debates, discussions, and deliberations.

Among its many themes and objectives EAU 2019 championed international co-operation with the Urology beyond Europe track. The first day of the congress played host to a number of joint sessions organised with a variety of national and multinational urological societies. The World Chinese Urologists, Arab Association of Urology (AAU), Korean Urological Association (KUA), and the Urological Society of Australia and New Zealand (USANZ), among many others, could be found at EAU 2019. Each of the joint sessions focussed on various aspects of urology, from practice patterns in different areas of the globe, as discussed at the joint USANZ–EAU session, to the in-depth discussion surrounding robot assisted laparoscopy highlighted during the joint World Chinese Urologists–EAU session. Medicine is a constant learning process, it is only through international co-operation that we can hope to achieve the best results for patients. Additionally, EAU 2019 saw the launch of the World Bladder Cancer Patient Coalition, which has been formed as a result of collaboration between a number of bladder cancer groups. The World Bladder Cancer Patient Coalition aims to improve care, information, and research for the 2.7 million people living with bladder cancer across the globe. Read more about the goals and work of the coalition in a special feature by Lydia Makaroff, CEO Fight Bladder Cancer.

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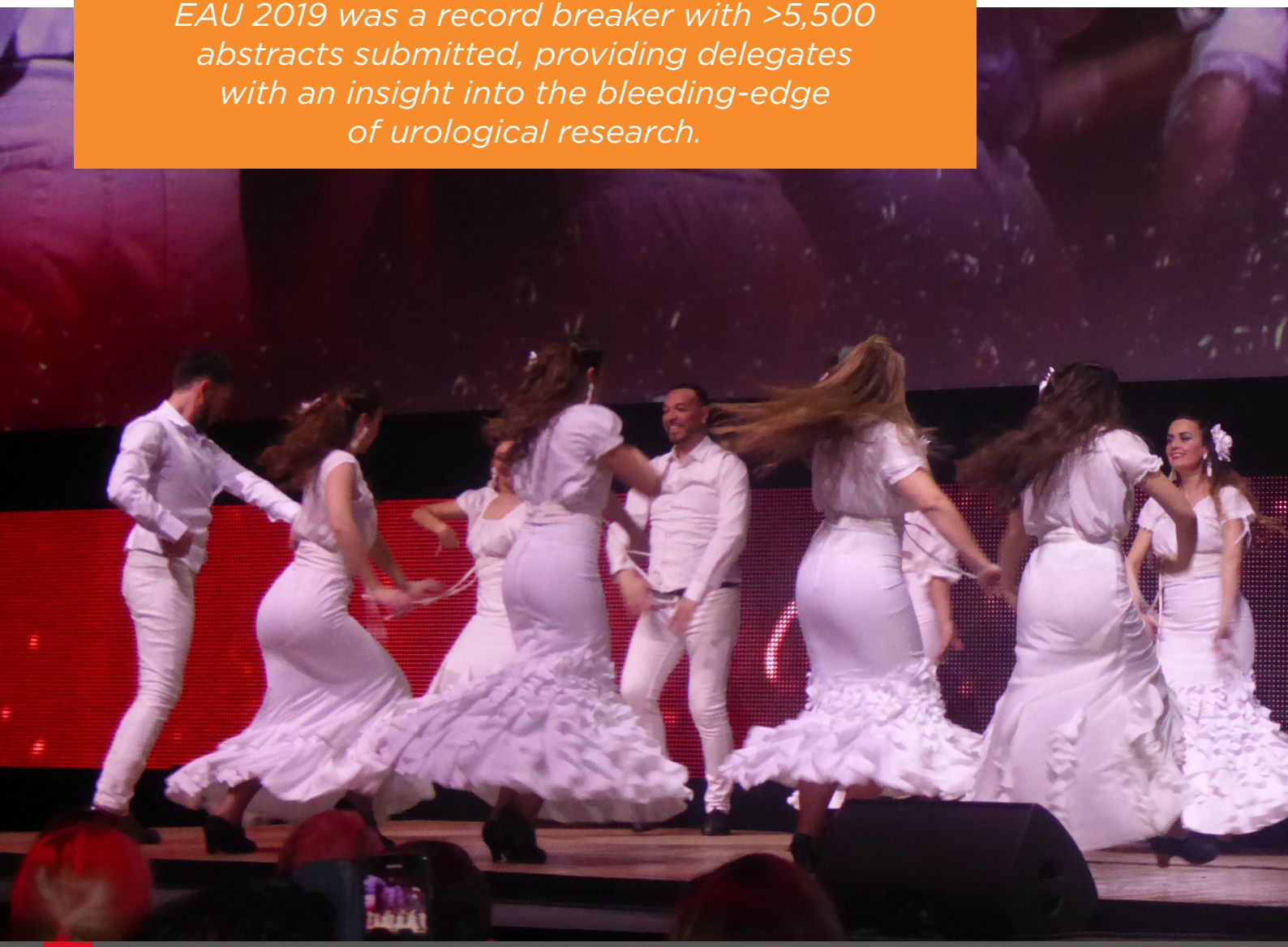
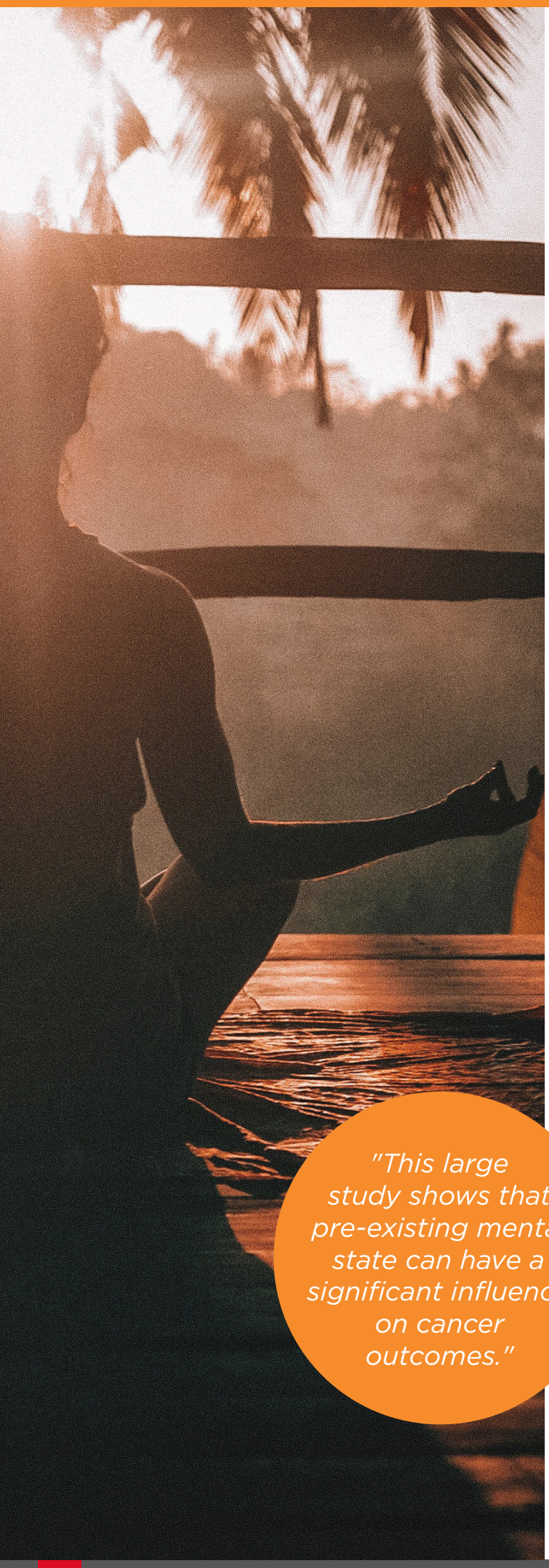


As ever, EAU 2019 was abuzz with late-breaking new stories, abstracts, and research. The key highlights from the congress can be found within the pages of the journal, including details of numerous research studies and trials. Further evidence linking working the night shift with an increased need to urinate has been highlighted by Italian researchers, while a Japanese team have linked substances in coffee with an inhibition in the progression of prostate cancer. Details of these and much more fascinating research can be found within the comprehensive congress review.

With a spectacular EAU Annual Congress now behind us, and with an eye firmly focussed on what promises to be a thrilling year of urological research and discovery, the EMJ team is already looking forward to attending the next EAU Annual Congress, which will be held amid the canals of Amsterdam, Netherlands, in March 2020.

EAU 2019 REVIEWED →



Mental Health State Associated with Higher Death Rates for Prostate and Other Urological Cancers

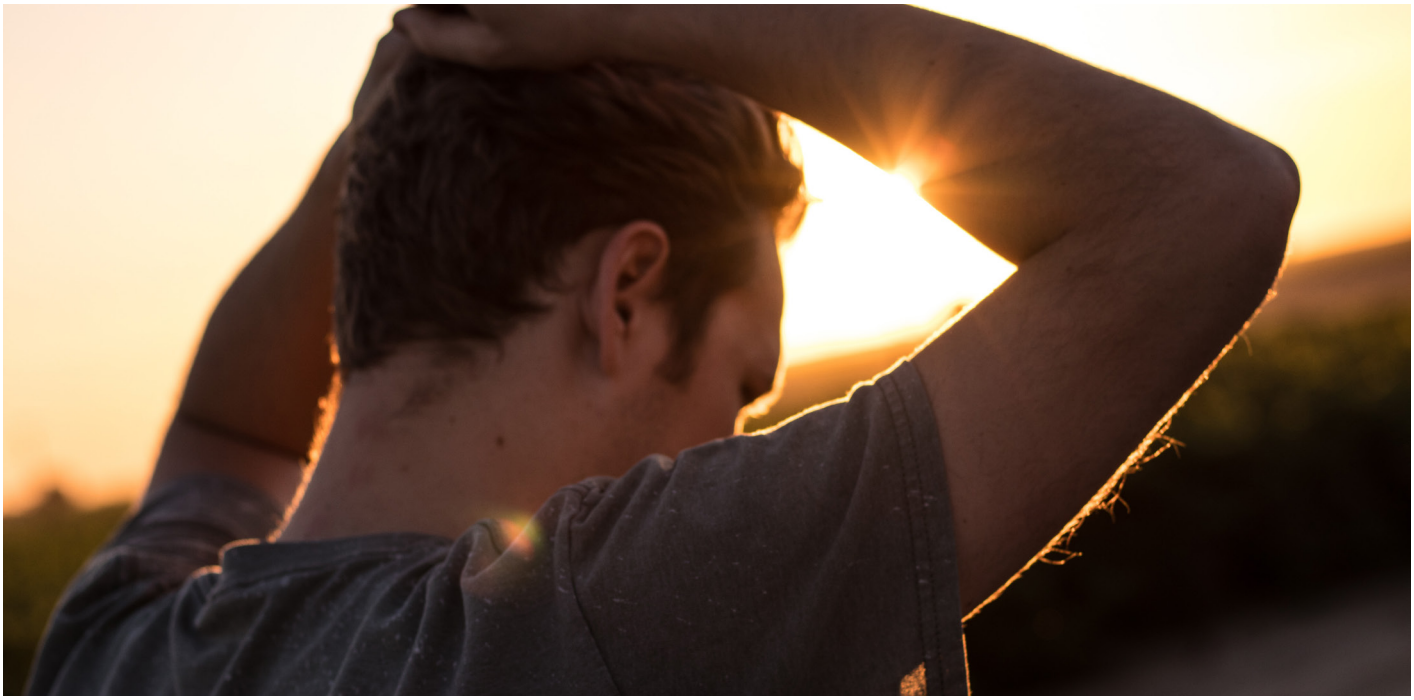
PATIENTS with urological malignancies are at greater risk of dying if they have a history of psychiatric care and, compared to the general population, show an increased risk of suicide. This message was delivered by Prof Zachary Klassen to attendees of the EAU Congress and reported in a EAU press release dated 18th March 2019.

The USA and Canadian team analysed the mental health records of 191,068 Ontarians being treated for either kidney, prostate, or bladder cancer. A score was assigned to each denoting their use of psychiatric services within the last 5 years, creating a mixed cohort that could be compared against control patients who were cancer-free.

The researchers found that the degree of prior mental health treatment was directly correlated with an increased mortality rate in these patients, amounting to a 1.78-times decrease in survival rate. Additionally, when suicide rates for these patients were researched following diagnosis of these cancers, a 16% increase was highlighted in the whole cohort compared to the general population. Interestingly, there was a 39% increase in suicide risk in patients with no history of impaired mental health, suggesting that diagnosis alone is enough to severely influence these patients' mental wellbeing.

"This large study shows that pre-existing mental state can have a significant influence on cancer outcomes."

Prof Francesco Montorsi, Adjunct Secretary General of Science for EAU, commented: "This large study shows that pre-existing mental state can have a significant influence on cancer outcomes. In addition, it shows that just the diagnosis of cancer can have a bearing on whether or not the patient attempts suicide. The clinical community has a duty to treat the whole patient, not just the cancer, so we need to take note of these findings and where possible to include appropriate precautions to take account of a patient's mental health history."



Hormonal Treatment May Trigger Depression in Men with Prostate Cancer

FOLLOWING prostatectomy, the commencement of anti-hormonal treatment correlates with an 80% increase in depression rate in prostate cancer patients, leading to the recommendation that post-surgical monitoring should become the norm for all of these men. These findings were presented at the EAU Congress by a Danish team led by Dr Anne Sofie Friberg, Rigshospitalet, Copenhagen, Denmark, and reported in a EAU press release dated 28th March 2019.

"The reason could be either a consequence of failing surgery, directly caused by the hormonal manipulation, or both."

The records of 5,570 patients from the Danish Prostate Cancer Registry were analysed, 773 of whom had been treated post-surgically for depression. Additional treatment with anti-hormone therapies, commonly offered to the 25% of relapsed patients, correlated with a 1.8-fold increase in depression susceptibility.

It is now commonly accepted that cancer diagnoses can often lead to onset of depression. The researchers noted that, regardless of anti-hormone treatment, prostatectomies increase depression risk. Speculating on the reasons why anti-hormonal treatment led to a higher incidence of depression, the researchers suggested that the inhibition of testosterone production can result in worsening the litany of side-effects caused by prostate removal. These include urinary incontinence, erectile dysfunction, loss of libido, and altered body image. They suggested that this could lead to increased depression and also commented that the low testosterone levels might be influencing the brain's mood centres.

"The reason could be either a consequence of failing surgery, directly caused by the hormonal manipulation, or both," commented Dr Friberg. The team believes the robustness of the data emphasises how oncological treatments can influence various other aspects of patient health and that prostate cancer clinicians must adopt a long-term, multidisciplinary approach to provide the patient with care that is as comprehensive as possible.

"...those patients who show a greater tendency towards neuroticism have worse outcomes 3 years after prostate cancer surgery."

Neuroticism Linked to Poorer Recovery from Prostate Cancer Surgery

MEN who score highly for neuroticism are more likely to have adverse effects following prostate cancer surgery, including erectile dysfunction, bowel problems, and incontinence. Researchers from Norway have found that differences in prostate cancer surgery outcomes, previously thought to be due to variances in surgery and circumstances of cancer, may also be due to the personality trait neuroticism. This was reported in a EAU press release dated 16th March 2019.

In 2011, researchers gave questionnaires to 982 men who had been treated with radical prostatectomy at Oslo University Hospital, Oslo, Norway, between 2005 and 2010. They had a response rate of 79%, receiving 777 questionnaires, 761 of which reported on postoperative adverse effects and neuroticism. Of the responding men, 22% scored highly for neuroticism, which was found to be correlated with significantly lower scores regarding recovery from the radical prostatectomy.

The researchers concluded that adverse effects 3 years following radical prostatectomy were strongly associated with high levels of neuroticism. Around 20–25% of men in developed countries have high neuroticism, and the researchers believe that cancer teams should give patients preoperative personality tests to ensure they are receiving the best and most appropriate care.

Lead researcher Dr Karol Axcrona, Akershus University Hospital, Lørenskog, Norway, discussed the neuroticism and the implications of the study: "Neuroticism is not an illness, but a basic personality trait, like extraversion or openness; we all have some degree of neuroticism. What we found was that those patients who show a greater tendency towards neuroticism have worse outcomes 3 years after prostate cancer surgery. This is a real effect, and doctors need to take account of this, in the same way that we would take physical factors into account before and after cancer treatment. This means we may need better advance personality testing for identification and counselling, and perhaps a more specialised follow-up of those men who might be at risk of poorer outcomes."

Sperm Extracted from Testes May Offer New Treatment Options for Infertile Men

SPERM taken directly from the testicles of infertile men has better DNA integrity than that of their ejaculated sperm, suggests new research revealed in a press release from the EAU congress in Barcelona on the 17th March 2019. The scientists also found that the testicular sperm was as good as the sperm ejaculated by fertile men.

The study compared the testicular and ejaculated sperm from 63 infertile men who displayed persistent DNA fragmentation, and who had failed cycles of intracytoplasmic sperm injection, and compared these with the sperm from 76 fertile volunteers. Researchers used the Comet assay to measure single and double strand breaks in the DNA. They found that damage to ejaculated sperm DNA was higher in infertile men, who displayed 40% damage, than in fertile men, who showed 15% damage. However, they were surprised to find the sperm taken directly from the testicles of infertile men was of a similar quality to the ejaculated sperm from fertile participants.

Prof Sheena Lewis, Emeritus Professor Queens University, Belfast, UK, discussed the study: "What this means is that the DNA in sperm from the testicles of infertile men are better quality than sperm from their ejaculates. This opens the way to taking sperm directly from the testes of men who have highly fragmented ejaculated DNA and failed cycles of treatment and trying to achieve fertility with these testicular sperm. We also noted in a subgroup that the amount of the more serious double stranded DNA breaks was lower in the sperm taken from testicles, so using these sperm is more likely to lead to an improvement in male fertility."

Infertility affects 1 in 6 couples across Europe and male infertility is the most common reason for couples to seek fertility treatment. Evidence suggests that the integrity of DNA in the sperm is associated with miscarriage and failure of implantation. While this research is promising for couples with infertility issues, the researchers noted the need for confirmation of improved fertilisation rates and take-home-baby rates before this strategy is implemented.

"This opens the way to taking sperm directly from the testes of men who have highly fragmented ejaculated DNA and failed cycles of treatment and trying to achieve fertility with these testicular sperm."

Working Night Shifts Leads to an Increased Need to Urinate

MILLIONS of people across the globe work night shifts, with 3.2 million employees working during the night in the UK alone. Research over recent years has regularly shown links between working night shifts and greater risk of developing depression, cardiovascular disease, and certain cancers. New work presented in an EAU press release dated 16th March 2019 has discovered a link between working at night and an increased need to urinate.

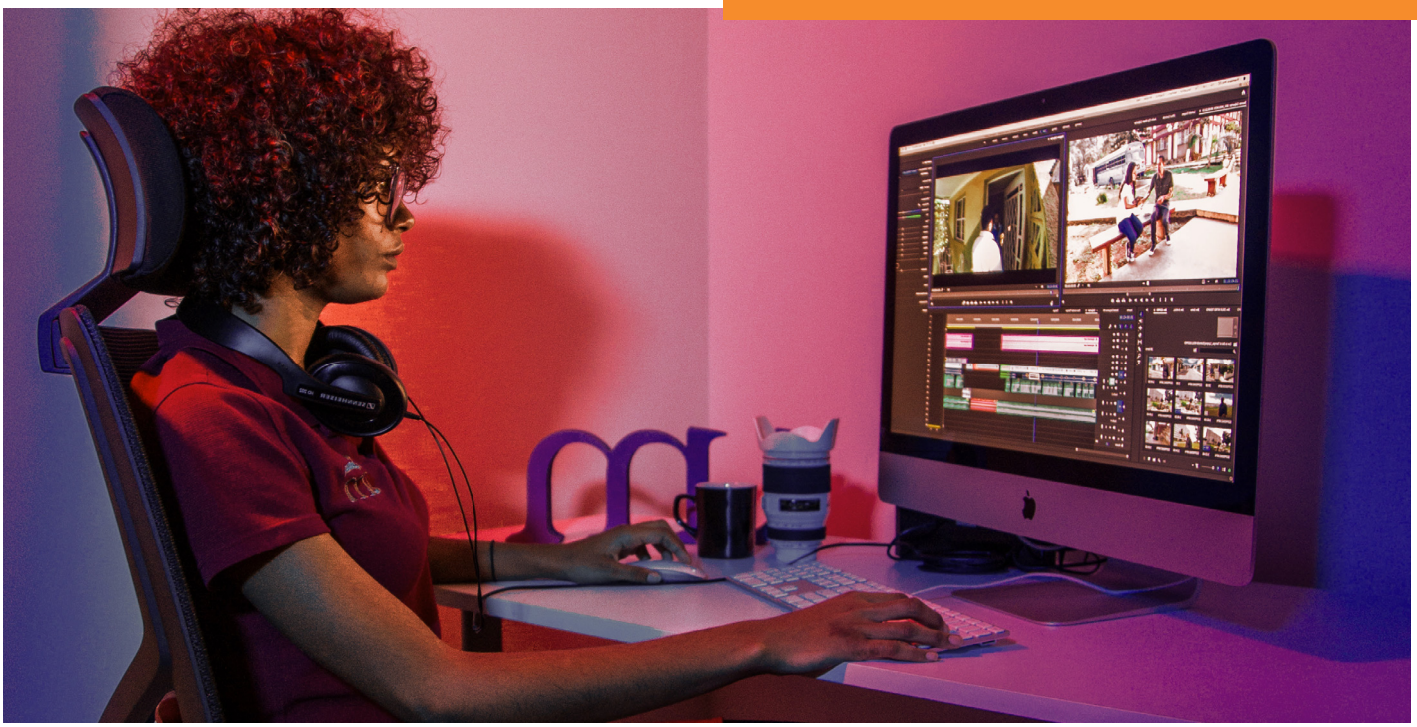
Conducted at the Sant' Andrea Hospital, Rome, Italy, between March and October 2018 the study, overseen by Dr Cosimo De Nunzio, recruited 136 volunteers (68 males and 68 females) with an average age of 40 years and a mean BMI of 23.3. Of the participants, 66 worked night shifts, working an average of 11 hours a night. Volunteers completed the Overactive Bladder Questionnaire (OABq) and the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLC-C30), both of which are internationally validated questionnaires.

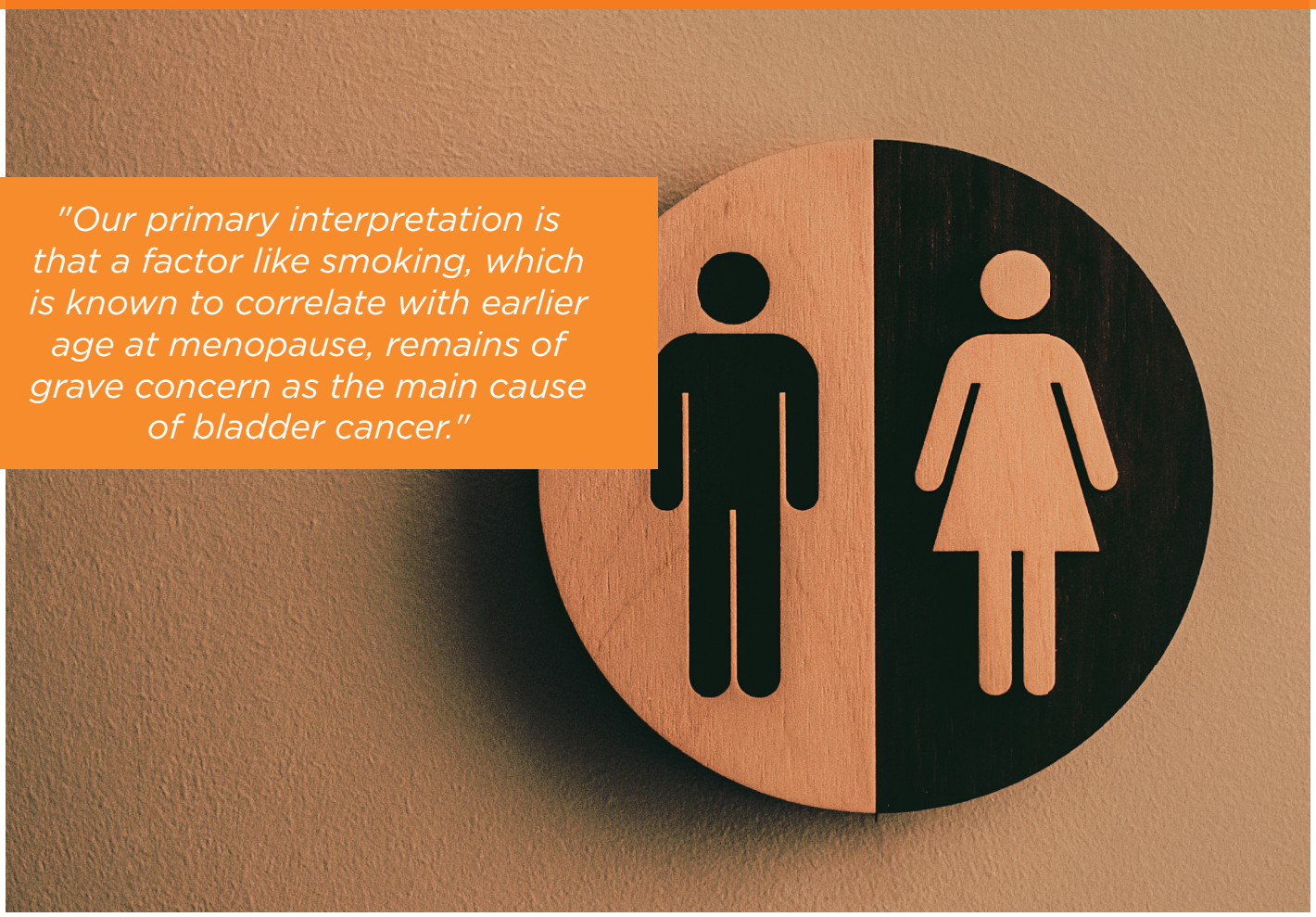
Analysis of the completed questionnaires showed that night shift workers reported a mean OABq score of 31 compared with a score of 19 reported by day workers. Additionally, night shift workers provided a mean EORTC QLC-C30 score of 41 compared with a score of 31 calculated from day shift worker responses. Dr De Nunzio summarised: "This work shows that constant night workers may have a higher urinary frequency as well as a decline in their own quality of life."

A concern raised by the authors was the age of the patients and their associated OABq scores. Traditionally, overactive bladder is associated with older patients, but the volunteers of this study were all <50 years old and are experiencing a deteriorating quality of life.

While this study is limited by its small size and the self-reported nature of questionnaire completion, the results highlight the important links between working night shifts and a deterioration in the quality of patient life due to urinary need.

"This work shows that constant night workers may have a higher urinary frequency as well as a decline in their own quality of life."





"Our primary interpretation is that a factor like smoking, which is known to correlate with earlier age at menopause, remains of grave concern as the main cause of bladder cancer."

Examining the Sex Difference in Bladder Cancer

PRESENTLY, there is a difference between the sexes regarding bladder cancer. While bladder cancer is more common in men than women, women are more likely to develop advanced bladder cancer and have worse survival outcomes than men, with the mortality rate in women approximately 40% higher. To better understand this disparity between the sexes, researchers from the USA and Europe conducted a prospective cohort study. This study was presented at the EAU Congress, as reported in a EAU press release dated 15th March 2019.

The study's lead author, Dr Mohammad Abufaraj, University of Vienna, Vienna, Austria, highlighted the study's primary finding: "We found that smoking women who experienced menopause before they were 45 years old had a greater risk of bladder cancer. Smoking remains the most important risk factor for bladder cancer." Dr Abufaraj also explained how other factors, such as number of pregnancies, oral contraceptive use, the use of hormone replacement therapy, and the age when periods began, had not been shown to be linked to the development of bladder cancer.

The study population comprised two cohorts: one of 106,138 female registered nurses and one of 113,974 female nurses. Over a 36-year follow-up period, those who underwent menopause aged ≤45 years old were found to be 41% more likely to have developed bladder cancer than those who underwent menopause aged ≥50 years old. This risk was increased in those women who had previously smoked, who, if undergoing menopause aged ≤45 years old, were 53% more likely to have developed bladder cancer than those who underwent menopause aged ≥50 years old.

Dr Abufaraj added: "Our primary interpretation is that a factor like smoking, which is known to correlate with earlier age at menopause, remains of grave concern as the main cause of bladder cancer. It reinforces the warning that smoking is really harmful in ways that we might not have imagined."

Coffee Compound Combo Could Halve Prostate Cancer Tumour Growth

COFFEE has a long history of medicinal use, and modern research has shown that it may have a variety of protective qualities. Adding to this body of work, new research from Kanazawa University, Kanazawa, Japan has, for the first time, shown that compounds in coffee may inhibit the growth of prostate cancer. The study results were made public in a press release from the EAU congress in Barcelona, Spain, on 18th March.

The researchers set out to explore some of the many compounds naturally found in coffee, testing six of them *in vitro* for their effect on cell growth. Two of these compounds, kahweol acetate and cafestol, were found to grow more slowly than controls; therefore, they were selected for study in a mouse model of prostate cancer. Sixteen mice received transplanted prostate cells before being divided evenly into four groups: one group treated with kahweol acetate, one treated with cafestol, one treated with a combination of kahweol acetate and cafestol, and one untreated control group.

Results showed the inhibition of cancer cell growth in both the kahweol acetate group and the cafestol group, but the greatest finding came in the combination group: "The combination seemed to work synergistically, leading to a significantly slower tumour growth than in untreated mice," explained the study leader, Dr Hiroaki Iwamoto, Kanazawa University. After 11 days, the combination-treated group were found to have around half as much tumour growth as the untreated group (167% growth versus 342% growth, respectively).

Since this was a pilot study, the authors urged caution when considering these results, but are hopeful that they will soon be able to test these findings in a human model. "Coffee can have both positive and negative effects (for example, it can increase hypertension), so we need to find out more about the mechanisms behind these findings before we can think about clinical applications. However, if we can confirm these results, we may have candidates to treat drug-resistant prostate cancer," concluded Prof Atsushi Mizokami.

"...if we can confirm these results, we may have candidates to treat drug-resistant prostate cancer..."

Positive Results Seen on Prostate Cancer Recurrence Following Testosterone Therapy

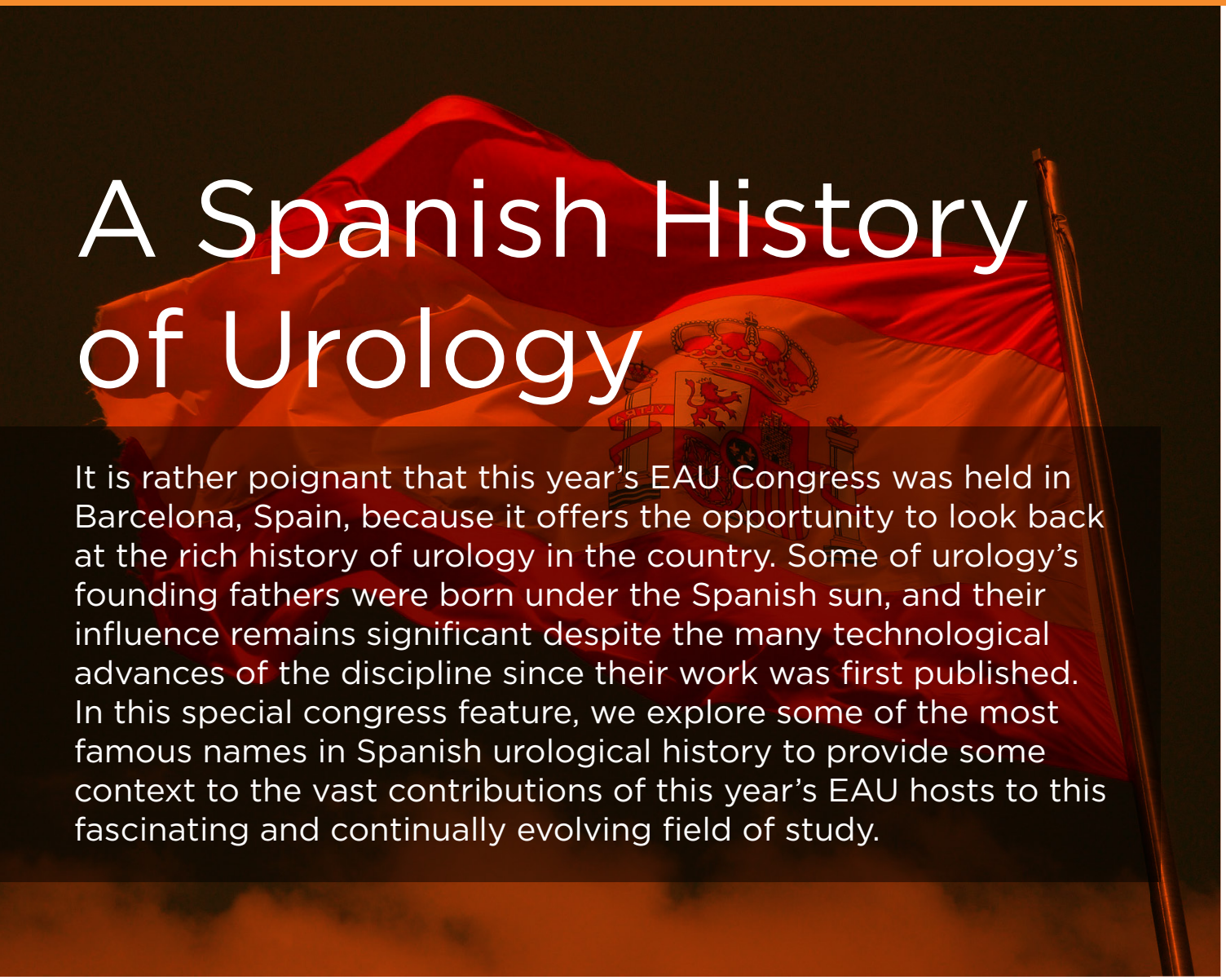
NOBEL PRIZE-winning research from the 1960s on the effects of testosterone on prostate cancer has had new light shed on it by the results of a recent study that took place at the University of California, Irvine, California, USA.

Traditionally thought to reduce the risk of prostate cancer, medications that reduce the level of testosterone have become a commonplace treatment for patients. However, towards the end of the 20th century it was noted that these patients were instead dying prematurely from cardiovascular disease, since the testosterone treatment was causing complications in metabolic processes, for example, the patients had a higher incidence of diabetes, mid-abdomen visceral fat, and elevated cholesterol, while simultaneously reducing the risk of developing prostate cancer.

"...this puts us at the stage where we need to question the taboo against testosterone use in prostate cancer therapy..."

With this observation in mind, the research group at the University of California selected 834 patients for a study into testosterone replacement therapy (TRT) to improve sexual function following radical prostatectomy; 152 of these patients had no evidence of disease and were treated with TRT. All patients were tested after a median of 3.1 years post surgery for signs of biochemical recurrence of disease in their prostate-specific antigen (PSA) levels. Results showed that approximately 5% of patients in the TRT subgroup had disease recurrence whereas 15% of untreated patients had experienced a recurrence of the cancer. After the team had adjusted the results for pathological grade and stage, it was found that TRT was linked to a longer time to biochemical recurrence and also delayed progression of the recurrence by a median of 1.5 years.

Commenting on the study, group leader Prof Thomas Ahlering, University of California, explained: "This was not what we set out to prove, so it was a big surprise: not only did testosterone replacement not increase recurrence, but it actually lowered recurrence rates. While the testosterone is not curing the cancer per se, it is slowing the growth of the cancer, giving an average of an extra 1.5 years before traces of cancer can be found." He added "There have been smaller studies which have hinted that testosterone may not be risky for certain patient groups, but this is the largest such study ever conducted. We're not suggesting that treatment methods be changed just yet, but this puts us at the stage where we need to question the taboo against testosterone use in prostate cancer therapy, especially for low-risk patients after radical prostatectomy."



A Spanish History of Urology

It is rather poignant that this year's EAU Congress was held in Barcelona, Spain, because it offers the opportunity to look back at the rich history of urology in the country. Some of urology's founding fathers were born under the Spanish sun, and their influence remains significant despite the many technological advances of the discipline since their work was first published. In this special congress feature, we explore some of the most famous names in Spanish urological history to provide some context to the vast contributions of this year's EAU hosts to this fascinating and continually evolving field of study.

JULIAN GUTIERREZ DE TOLEDO

Gutierrez de Toledo was a Spanish urologist whose works in the 1400s continue to be highly regarded by urologists for their accuracy and for the picture they paint of the urological field at that time. In 1494 he printed a Latin text presenting the prevalent opinions at the time of physicians including "Hippocrates, Galen, Avicenna, Razis, and all others".[1] In addition, he authored the earliest known printed text in the Castilian language, on the topic of "Cure of the stone and pain in the loin and/or renal colic".[2] This text presents a comprehensive report of the understanding of urological diseases in the Middle Ages and, interestingly, the teachings differ very little from our modern interpretation of these diseases; for example, his description of where a kidney stone may appear: "Sometimes at the beginning next to the kidney, sometimes in the narrow middle, sometimes in the mouth of the bladder neck, and sometimes in the pipe of the phallus."[1]

FRANCISCO DIAZ

Truly one of the giants of the urology discipline, Diaz printed a number of texts in his lifetime that are considered to have shaped both historical and modern understandings of a variety of urological disorders and their treatment. His 1588 text 'Tratado Nuevamente Impreso de Todas las Enfermedades de los Riñones, Vejiga y Carnosidades de la Verga y Urina, dividido entres libros' (Newly printed treatise of all the diseases of the kidneys, bladder and carnosities of the phallus and urine, divided into three books) draws together both academic and practical information for physicians, surgeons, and students of anatomy.[3] The text deals in particular with the treatment of strictures of the urethra, which Diaz strongly recommended be treated

early using a tool named the 'instrumento cisorio', a device that cuts away protruding flesh of the urethra to avoid the unpleasant complication of urine suppression.[3]

As we direct our gaze closer to modern times, another pre-eminent Spanish urologist stands out as an exceptional influence: Salvador Gil Vernet.

In addition to its scientific validity, the language and syntax of the text itself provides a fascinating insight into Diaz's life at the time. A study performed in 2003 discovered that 543 of the medical terms in the treatise were original contributions from Diaz, not found in contemporary lexical dictionaries.[4] This demonstrates not only his unparalleled knowledge of the urological field at the time, but also the contributions he made to the progression of those ideas and their communication to a wide audience.[4] Diaz's significant contributions to urology are recognised in the Francisco Diaz medal, created by the Spanish Association of Urology in 1973 as an award for scientific, associative, or educational achievements.[1]

SALVADOR GIL VERNET

As we direct our gaze closer to modern times, another pre-eminent Spanish urologist stands out as an exceptional influence: Salvador Gil Vernet. Gil Vernet dedicated his life to the study of anatomy, with a focus on urological systems, in particular the purpose and function of each component of the prostate.[5] Gil Vernet's opinion was that an understanding of how anatomical systems work was the necessary expertise for any researcher, and that descriptions of the systems were not sufficient. His dedication to the discipline led to many advancements in the field and subsequent decoration with a myriad of awards and honours across his lifetime. Quite possibly his greatest achievement is his publication 'Patología Urogenital', widely considered one of the most prestigious Spanish contributions to urology. The text is split into three volumes, discussing, amongst a number of other topics, important discoveries regarding the prostate gland and prostate cancer, including the key role that is played by diet, race, and genetics in the development of prostate cancer, and the origin of malignant neoplasms in the prostate gland itself as opposed to regions of benign prostate hyperplasia.[5]

The contributions of Spanish scientists continue to play a vital role in the progression and advancement of our understanding of urological diseases and their treatment. The discoveries and achievements listed above firmly place Gutierrez de Toledo, Diaz, and Gil Vernet among the giants of urology, but what remains to be seen is: who's next to join the ranks? With technological advancements getting more exciting every year, it is a great honour for the EMJ team to report on the EAU congress each year. We are already excited to be able to bring you more breaking news in next year's Congress Review.

References

1. Fariña-Pérez LA et al., Spanish Contributions to Urology – Historical Exhibition Brochure (2019), EAU, pp.2.
2. Virseda Rodríguez JA. [Julián Gutiérrez de Toledo and his book "Cure of the stone and pain in the loin and/or renal colic" in 1498]. Actas Urol Esp. 1994;18(3):165-77. (In Spanish).
3. Carrillo Esper R. [Andres Vesalio, Francisco Díaz, Miguel de Cervantes Saavedra and the birth of urology in the 16th Century]. Gac Med Mex. 2015;151(4):543-52. (In Spanish).
4. Moreno Torres A, Pérez Albacete M. [Urological terminology in Francisco Díaz: an example in the history of the Spanish language]. Arch Esp Urol. 2003;56(7):739-54. (In Spanish).
5. Gil-Vernet Sedó JM. Biography of Salvador Gil Vernet, eminent urologist anatomist (1892-1987). Pelviperineology. 2018;37:93-6.

Congress Feature

The Nightmare Stones Session

This year's EAU Congress featured a variety of innovative session formats, with the intention of providing all attendees with new and engaging ways to learn. The following session, suitably dubbed the 'Nightmare Stones Session', was one such format, offering a platform for Dr Marcel Fiedler to share a difficult case of laser lithotripsy that resulted in severe sepsis. The case was then cross examined by Mr Bertie Leigh, a medical lawyer and expert in medical litigation, who shed light on the legal connotations for the medical team. Finally, Dr John Denstedt was called upon to give his expert opinion about how this case should have been handled, before handing over to the audience for a brief Question and Answer session.

All medical procedures, particularly invasive ones, carry a risk of complications and it is only through sharing details of the most challenging cases that the medical society can learn and develop for the benefit of patients worldwide. While this session makes clear that, as Dr Denstedt highlighted, nothing is ever completely certain in medicine, it also emphasised that a lack of, or lack of adherence to, best practice guidelines can lead to difficulties.

THE PATIENT

The patient was a 56-year old female presenting with a renal stone in the left renal pelvis measuring 21 mm and three smaller stones (9 mm, 6 mm, and 4 mm) in the left lower calyx. She was a recurrent stone former, having had extracorporeal shock wave lithotripsy in both the 1980s and 1990s, as well as percutaneous nephrolithotomy (PCNL) of the right kidney. She had received extracorporeal shock wave lithotripsy of the left kidney in 2012.

THE CASE

Various treatment possibilities were discussed with the patient, who refused PCNL due to her previous bad experience with the procedure. Thus, flexible ureteroscopy was decided upon and pre-stenting was performed.

Day 1: The patient returned in 2 weeks, her urine and blood were tested and showed no signs of infection; therefore, the medical team performed flexible uretero-renoscopy (fURS) with laser lithotripsy; they dusted the larger stone in the renal pelvis and fragmented and removed the smaller stones in the lower calyx.

The procedure was uneventful and lasted for 118 minutes, after which a double J stent was placed, and an antibiotic prophylactic regimen was started.

That night, the patient developed a fever and shivering. White blood cell count and urine tests showed signs of infection. However, a chest X-ray was performed, and the results

were unremarkable. Sonography was used and confirmed that the stent was positioned correctly. A follicle catheter was inserted to prevent reflux of urine through the stent.

Day 2: The patient still had a fever and their pulse had quickened.

Day 3: The patient rapidly deteriorated, with pulmonary function worsening, and she was moved to the intensive care unit. Tests showed multisensitive *Escherichia coli* in the urine and the blood. A chest X-ray once again ruled out pneumonia.

Day 5: The patient experienced pulmonary insufficiency and was intubated. A chest CT revealed pneumonia.

Day 8: The patient had developed acute kidney failure, which was hypothesised to be a result of multiorgan failure due to sepsis. As a result, dialysis was started. Creatinine levels were initially normal, but then went up to 6 or 7.

Day 10: The patient had deteriorated further, with gangrene of peripheral fingers/toes requiring surgery.

Day 18: The patient finally left intensive care. The double J stent was removed 7 days later, and the patient was discharged 1 month from the start of treatment. Continued dialysis was required.

THE CROSS EXAMINATION

Mr Leigh was invited to question Dr Fiedler about the case and did so forensically, highlighting areas of the treatment regimen which could be the basis for legal action on behalf of the patient.

Mr Leigh began by pointing out that the stone situated in the renal pelvis was very large, to such an extent that fURS was contraindicated. Dr Fiedler replied that while PCNL is the best option, guidelines show fURS to be the second-best choice. Mr Leigh retorted that this case ultimately represented an incidence of patient preference leading the clinicians to perform a procedure which they knew was inferior. In response, Dr Fiedler added that while stone clearance rate is better in PCNL, the literature shows that fURS can be a reasonable option in larger stones and does not necessarily have a higher complication rate than PCNL.

Mr Leigh's next line of inquiry regarded the use of antibiotics, or, importantly, the lack thereof. Dr Fiedler referred to guidelines when asked why his team did not administer preoperative antibiotics to the patient, noting that the guidelines also recommend perioperative administration.

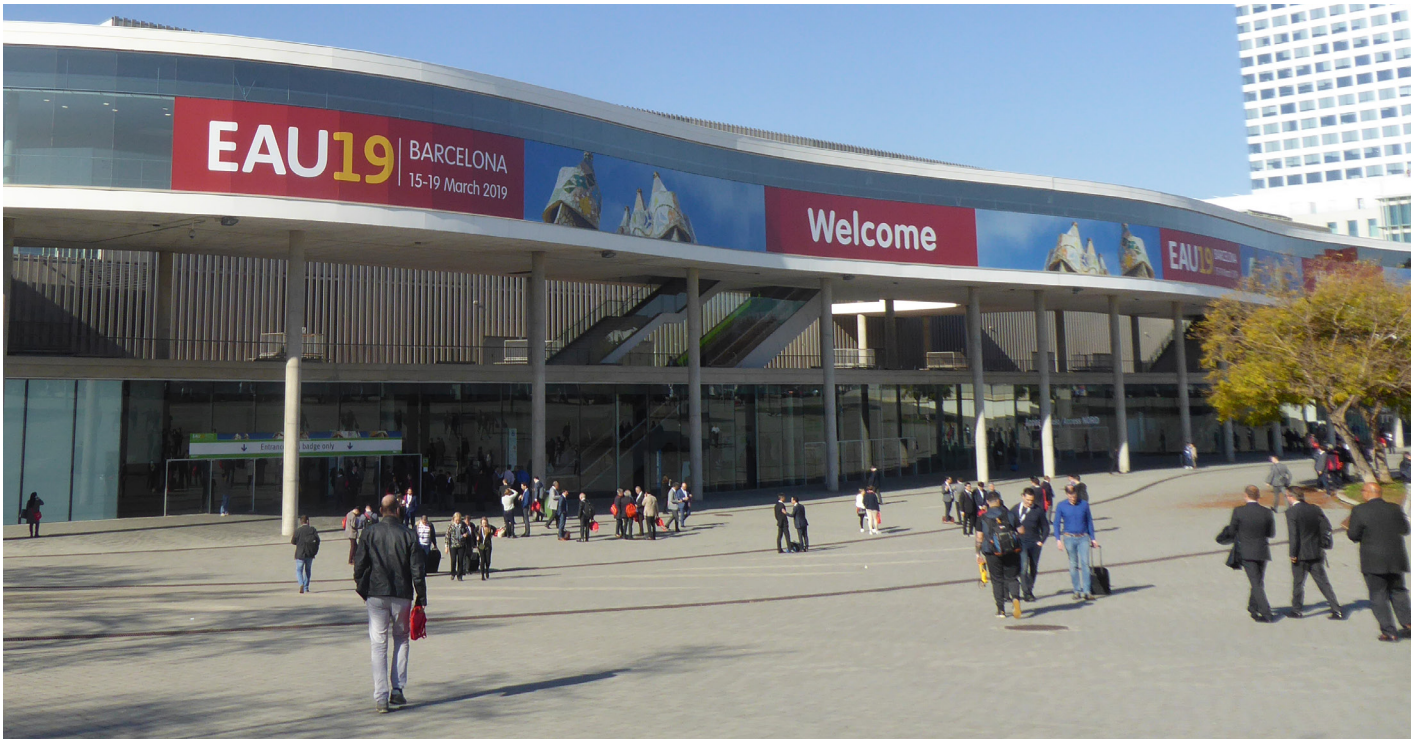
The extended duration of the procedure was also a cause for concern. Mr Leigh noted that the upper limit of safety for laser lithotripsy is 90 minutes, but this procedure continued for 118 minutes. Dr Fiedler defended his team's decision by arguing that prolonging the treatment avoided the need for a second procedure to complete the lithotripsy, therefore preventing complications associated with anaesthesia. However, Dr Leigh countered this point by stating the incredibly low mortality rate associated with uncomplicated, elective anaesthesia.

> ...it is only through sharing details of the most challenging cases that the medical society can learn and develop for the benefit of patients worldwide.

Finally, Mr Leigh also lamented that no microbiologist was consulted with a full patient history and, instead, the clinicians awaited the results of urine and blood cultures.

ADDITIONAL DISCUSSION

Dr Denstedt evaluated the case in further detail, considering what the best-case practice would have been. He initially commented that both EAU and American Urological Association (AUA) guidelines stated that PCNL was the procedure of choice for stones >2 cm. As the patient had presented with a stone volume of at least 3–4 cm, Dr Denstedt suggested that the patient might have been treated with the wrong procedure and that the treatment options should have been discussed in more detail with the patient. Having said that, he conceded that flexible ureteroscopy was growing in popularity for larger stones and that the envelope was increasingly being pushed in this regard.



Moving on, Dr Denstedt homed in on sepsis as the real issue with the presented case. He discussed that although sepsis typically had a low incidence rate, its associated mortality rate was high and therefore it was crucial to understand some of the risk factors for sepsis. Some of the risk factors he highlighted were:

- Lengthy operation (>90 minutes).
- If the patient has diabetes or other comorbidities.
- Stent put in ahead of time.
- A positive urine culture.

Dr Denstedt then explained that there were several practices, or lack of practices, in this case that had increased the risk of postoperative sepsis. There were no prophylactic antibiotics and a stent was put in ahead of time.

> The patient had developed acute kidney failure, which was hypothesised to be a result of multiorgan failure due to sepsis.

Further discussing prophylactic antibiotics, Dr Denstedt declared that the lack of antibiotic prophylaxis in this case was not ideal. He drew on the EAU and AUA guidelines as evidence, which both recommend the use of prophylactic antibiotics. Dr Denstedt said that the debate was really whether the antibiotics should be delivered intravenously or orally and that, in his practice, they used a single dose of intravenous antibiotics prior to the operation. On this note, Dr Denstedt urged the audience not to overuse antibiotics, suggesting that urologists were probably still using too many doses.

Dr Denstedt concluded by providing a summary of his main tips:

1. Ensure you obtain a preoperative urine culture and treat any infection.
2. Obtain a stone culture when possible. This may be more predictive of postoperative sepsis than a urine culture. However, it does take additional time after the operation to get the results of a stone culture and it may not always be practical to wait.
3. Avoid routinely stenting the patient.
4. Keep kidney pressure down. In Dr Denstedt's practice, the clinicians consider doing this when the patient is suspected to be at high risk of developing sepsis.
5. Ensure operation times are not overly long.

REAL-WORLD PRACTICE

The natural uncertainty inherent to the practice of medicine was highlighted when Mr Leigh

challenged the attendees on whether they would cancel the operation if results from a urine culture were not available. With most of the audience stating they would continue with the operation if the results were not available, Mr Leigh questioned this practice and the value of the urine culture.

Dr Denstedt interjected at this point, noting that nothing was ever completely certain in medicine and, furthermore, not every patient should be treated in the same way. He gave two contrasting examples:

1. A young totally healthy individual with no prior history of infection.
2. A patient with diabetes and a history of infections in the past.

Dr Denstedt noted that it would be far more plausible to proceed with the operation without results from a urine culture in the case of the first patient.

However, it was noted that one should blend such a patient-specific approach with due regard for the relevant guidelines. Dr Denstedt highlighted that although personalised medicine was currently a very hot topic, in his experience, failure to standardise approaches led to uncertainty and problems later on. He specifically pointed to the case that had been presented, noting that the guidelines gave clear recommendations.

AUDIENCE QUESTIONS

Q1 Is there any definition of an operation time that is 'too long'?

Dr Fiedler acknowledged that this was a pertinent question and that this issue came down to good clinical practice rather than evidence. He turned to Dr Denstedt for an explanation of his own practice. Reflecting on this, Dr Denstedt commented that patients were presenting with larger and larger stones and longer ureteroscopy operations were being conducted. In his practice, it was felt that 90 minutes represented the limit. After this, he believed that complication rates, such as sepsis, began to increase. Therefore, he would tend to end an operation by the 90-minute mark and bring a patient back 2–3 weeks later if necessary.

Q2 I think we all agree that urine cultures are important beforehand. However, what about the timing of those cultures? In real-world practice, sometimes the culture can be 3 months beforehand. What do you do in that situation?

Dr Denstedt agreed with the significance of this point. He highlighted that, in his own practice, the pre-admission programme was designed so that the culture was conducted a week before. However, if the aforementioned situation were to arise, he believed another culture should be taken as there was too much of a risk that the situation could have changed over 2–3 months.

Q3 If I use my own previous experience as a justification for my practice (e.g., this has worked for X number of patients), how do I stand from a legal perspective?

Mr Leigh strongly rebuffed the idea that this would be a suitable legal defence. He answered that lawyers would ask medical experts to advise them in such an instance and that the experts would tend to base their responses on the results of large, double-blind clinical trials rather than anecdotal evidence from individual practitioners.

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*DeFoor et al. 2017. J Pediatr Urol. 2017;13(4):373.e1-373.e5.

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Congress Interview

Prof Dr Hendrik Van Poppel

Adjunct Secretary General of the EAU
responsible for Education

At EAU 2019, it was our pleasure to meet with the venerable Prof Hendrik Van Poppel, the Adjunct Secretary General of the EAU responsible for Education, to discuss all things urology. This candid interview covers Prof Van Poppel's extensive career, including the origins of many of his famous surgical innovations, as well as the import role he played in developing this year's EAU programme. Whether you are seeking insight into the EAU's development or the role of robotic laparoscopy in the future of urology, you need look no further than this world-renowned specialist.

Q1 You have worked within the field of urology for >35 years, how has the field changed since you first became involved and what is the most exciting advancement you have seen?

I started my career in urology in 1980, at a time when urology was mainly endoscopy, minor genital surgery, varicoceles, circumcision, stone retrieval with Dormia extractions, and transurethral resection of the prostate and of bladder tumours. Over time, we have become a major surgical discipline and developed big surgical techniques, such as cystectomies and urinary diversions. When I started in this field, if we had a diversion to perform, we would ask the abdominal surgeons to do it, but today urologists are handling vena cava thrombosis, retroperitoneal lymph node dissection, intestinal surgeries, and more. We began as endoscopists and very minor surgeons, became major surgeons, and now we are arriving in a minimally invasive surgical era with robot-assisted laparoscopy. Endoscopy is once again becoming more important. I would say this is the most important change in the last 30–35 years.

Q2 In 2017, the European Prostate Cancer Centres of Excellence (EPCCE) was developed as a result of numerous conference calls, emails, and the EAU Prostate Cancer Centre Consensus Meeting. How important do you believe programmes, such as the EPCCE, are to modern medicine?

Last year at the European Multidisciplinary Congress on Urological Cancers (EMUC) congress, we had the EPCCE consensus meeting, where we involved urologists, radiologists, radiation

oncologists, nuclear medicine experts, patients, nurses, psychologists, and medical oncologists. We aimed to conclude just what a centre of excellence for prostate cancer should really stand for. The most important thing is the care for the patient, but secondary to this is education and thirdly the research. The centre needs to have the research and education facilities, and they should be able to offer all possible diagnostic and therapeutic options. This level of access is currently reserved for a happy few throughout Europe, around 15–20 centres. These centres will be the top stars in this field and, for research and co-ordinating research, it would be very nice to have a network of these centres of excellence for prostate cancer.

"...the frame of urology is much larger than just surgery"

Q3 Is the example set by the EPCCE translatable to other cancers and diseases?

Beyond the initiative of the EAU, where we have involved many other disciplines, there are other initiatives too; they are not on the EPCCE, but on essential requirements. For instance, the Essential Requirements for Quality Cancer Care from the European Cancer Organisation (ECCO), which EAU has been working closely with, to define exactly what a European patient should receive when it comes to clinical cancer care. Is there psychological support? Is there the involvement of a multidisciplinary team? So, this is a completely different accreditation or recognition of centres and can be applied to other diseases, especially cancers.

Q4 You were recently involved in a study to identify the optimal candidate for salvage lymph node dissection for nodal recurrence of prostate cancer. What would you say is the take-home message from this study?

We are doing more and more aggressive surgery for prostate cancer. We stopped doing radical prostatectomies in low risk prostate cancer; these patients instead undergo active surveillance and maybe have surgery later. But where we do more surgery is in high risk prostate cancer patients, and we are also doing salvage lymphadenectomy in patients that, after a curative treatment (whether that is radiation or surgery), relapse in the lymph nodes of the pelvis. We are still not sure what the correct place for lymphadenectomy is. Does it really prolong the patient's survival? Maybe not; we have not shown that yet. But if a patient relapses in the lymph nodes, what other treatment can we do? We can remove them, we can use radiation therapy, or we can give systemic therapy. This means we give androgen deprivation therapy. If we have a patient who relapses with steadily increasing prostate specific antigen (PSA) and we find disease in the lymph nodes using our new, very specific and sensitive diagnostic tools (such as PSMA PET/CT), we would avoid androgen deprivation therapy and use surgery instead. This would result in the reduction of PSA and everybody is happy; this may not impact on the overall survival of the patient, but it will certainly postpone androgen deprivation therapy. A number of these patients never relapse, so salvage lymphadenectomy may even be curative in some cases, but the majority do relapse.

In the end, all prostate cancer patients who die from the disease will be castrated (i.e., will have their androgens deprived) at a certain point in time, which greatly impacts quality of life. Thus, I believe that postponing the need for androgen deprivation therapy is, in and of itself, an argument for the use of these salvage procedures.

Q5 You are chairing the Renal Cell Carcinoma session at EAU 2019. What do you hope that attendees will learn as a result of this session?

This session that I will co-chair with Dr Grimm from Germany is on a variety of topics, the first of which is minimally invasive surgery. We believe that, today, if we can avoid giving the patient a very painful incision and perform procedures with minimally invasive tools, then this is much better, because the patient will experience less pain and will not experience late incisional complications. In expert centres, robot-assisted partial nephrectomy seems to be perfectly comparable to what we achieve with open

surgery. However, there are limits and these are what Dr Kuczyk will try to highlight, showing that we cannot always propose laparoscopic robot-assisted partial nephrectomy in every complex case. I think the audience will learn that there are limits to minimally invasive treatments for renal cell carcinoma.

The second topic asks: 'What is the place for ablative therapies for small renal masses?' Ablation of renal masses has been proposed for frail patients who cannot undergo the usual treatment. Patients that cannot have active surveillance and cannot have major surgery can benefit from ablative therapy: radiofrequency ablation or cryoablation. The latter is more complex and difficult and mostly needs laparoscopic approaches, but radiofrequency ablation is a minimally invasive technique that works in frail patients and probably also in patients with small tumours detected via imaging. Without access to randomised clinical trials showing benefits to ablative therapy compared to conventional therapy, we need to further consider it as an investigational treatment that will be increasingly applied even without evidence-based trials.

The next point is on the neoadjuvant and adjuvant treatments. We know that we have had interferon, IL-2, and 5-fluorouracil administered to patients with high risk, where we believed that the final outcome of survival would be better if we give these drugs after the surgery in an adjuvant fashion (actually it did not improve the final outcome). There are also the tyrosine kinase inhibitors and the mTOR inhibitors. There may be a place for these drugs, but we still do not know which person might benefit from adjuvant and neoadjuvant treatment. Neoadjuvant use is now certainly a possibility in immuno-oncology drugs that have become available, and they seem to be effective in renal cell carcinoma as well. We will need to further explore which patient may benefit from neoadjuvant immuno-oncological therapies, i.e., which patient is at high risk for later developing metastatic disease and may profit from these therapies. Dr Mir Maresma will give the latest update on which evidence is available today.

Q6 You developed a number of original surgical techniques, including the prepubic urethrectomy, percutaneous gastrostomy, lumbal splenectomy during orthotopic kidney transplantation, and of the Leuven 'N' pouch for bladder substitution. What led you to develop these techniques? What impact has your work had on the patient experience both during and after surgery?

I have indeed developed a number of surgical techniques that might carry my name, for instance the prepubic urethrectomy, and why I developed that technique is a funny story. I was a resident in urology. My professor was doing a cystectomy and was doing a diversion and it took him 4–5 hours to do the procedure. Then he said: "Van Poppel, now you do the urethrectomy." This meant I had to close up the patient, reinstall the patient in the lithotomy position, make a perineal incision, and take the urethra out prophylactically in patients that had a high risk of urethral recurrence. I was already tired myself and then I thought maybe we can get that urethra out through another approach. Therefore, I prolonged the incision over the pubis, luxated the penis inwards, and did a prepubic urethrectomy without reinstallment of the patient. It turned out that it took just 20 minutes more, not half an hour or 1 hour longer, and it was safe. We had to cope sometimes with haematomas, but in the end the procedure as we do it today does not prolong the procedure. The patient has no pain perineally so it certainly has advantages.

The second procedure is the percutaneous gastrostomy. We know that patients in the postoperative period can vomit and can have gastroparesis. They can have paralytic ileus and then they are very uncomfortable with a nasogastric tube that needs to stay in place until the bowels start moving again. In this area today, we have early recovery after this important surgery with the ERAS protocol, but, at the time when I was trained, I hated having this tube in my patient's nose. We tended to remove it as soon as possible after the surgery because it was so unpleasant. Although I did not invent it (I have seen other surgeons, like Richard Turner-Warwick, putting tubes in the upper gastrointestinal tract), what I did at the

end of the procedure was inflate the stomach with air with the help of the anaesthesiologist and then put a bladder catheter into the stomach via puncture; it was left there until the patient was developing transit again and was removed after the patient had a normal breakfast without any complications such as peritonitis. So, I felt this was much more comfortable than the nasogastric tube. As I said, with the EUS protocol we have today, there is not too much indication to do this technique any longer unless the patient really needs to have an empty intestinal tract for several days.

Finally, there's the 'N' Pouch, which is simply a mixture between the Studer Pouch and the Hautmann Pouch; it's simply an 'N' pouch with an afferent limb. It's very fast. It doesn't take more than 1 hour. It is uncomplicated. It is a simple, termino-lateral insertion of the ureters on the afferent limb, like in the Studer pouch, and it is a very easy and fast procedure, which has been updated to include the results of >200 people.

Q7 In 2012, you held the position of EAU Adjunct-Secretary General. What was your greatest achievement in this role? If you held the role currently, upon which areas of urology would you focus the attention of the EAU Congress?

Since 2012, I have been the Adjunct-Secretary General and was responsible for education in the EAU after having been the director of the European School of Urology for 8 years prior. Education, in my opinion, is one of the most important tasks of the EAU. Education is at the heart of everything the European School of Urology is doing today at this congress. We have 55 courses, which are extremely well attended, mostly by younger urologists, on all the different topics that urology encompasses. Besides this, we have European School of Urology (ESU) courses at the national congresses of many countries; they ask us (two or three of the ESU faculty) to come and teach them. We have educational events at any meeting that the EAU is organising, whether this is on lower urinary tract symptoms, renal cell carcinoma, or prostate and bladder cancer. We also have educational events at the European Multidisciplinary Congress on Urological Cancers (EMUC) that we organise every year together with the European Society for Radiotherapy and Oncology (ESTRO) and the European Society for Medical Oncology (ESMO). There is hands-on training and training on MRI reading, as well as the training of radiation oncologists. So, we have a very important educational platform, not to mention a range of online education. I think the ESU today, under the guidance of John Palou, Barcelona, Spain, has become really tremendous and is a fantastic tool for education.

Q8 As someone who has worked in urology for >35 years, what advice would you give to someone who is just starting out?

After working in urology for >35 years, I would say to a young colleague that they have made the best choice. Urology is a wonderful profession and not only because it includes surgery. This is what the youngsters should absolutely know: the place of surgery, certainly in oncology, will not continue to increase, but it will decrease. Why? Simply because we have better medical treatments and radiation treatments than in the past. There are medical treatments that urologists have always been prescribing. We have always been treating infectious diseases, as well as lithiasis. We have always been doing androgen deprivation therapy and giving anti-androgens. We have been giving intravesical treatment with the cytostatic agents. So, urology is not only surgery and I would advise the younger ones that this is very important. There is not only surgery and there is not only robotic surgery, which attracts so many young people to urology. Do not forget that medical treatment of urological diseases, be they malignant or benign, is so important. We are not just surgeons. We are not doing surgery for an internist who indicates which patient should have which procedure. Rather, we see the patient for screening, for diagnosis of his disorder, we do all the endoscopic manoeuvres in diagnosis and treatment, and then treat the patient, not only with surgery but with drugs, with cytostatic agents, with immuno-oncological agents that recently became available, with targeted therapies... So, the frame of urology is much larger than just surgery and that would be my strongest advice to the young urologist. Do not forget this, because medical treatment will increase and will become more and more important in the care and cure of urological patients in the future.

Interview

Dr Giuseppe Salvaggio

Department of Biomedicine, Neuroscience and Advanced Diagnostics, Section of Radiology, University of Palermo, Palermo, Italy

Q1 What first drew you to a career in radiology?

My father is a radiologist, so I always wanted to work in radiology. During my time at medical school, I found that radiology was a wide field of study thanks to the different diagnostic imaging techniques, such as X-ray, ultrasound, CT, and MRI. I found them to be really exciting and I do not regret my choice.

Q2 In your experience, what do you think has been the greatest advance in recent years for urological radiography?

There is no doubt that it is prostate MRI. Before MRI, prostate cancer diagnosis was exclusively made using prostate-specific antigen levels, transrectal ultrasounds, and biopsies. Prostate MRI is a really well-functioning technique that allows great diagnostic confidence and avoids unnecessary biopsy. Moreover, it is comfortable enough for patients and presents almost no risks. I think it is really great.

"Collaboration occurs when individuals have mutual respect for one another, and one another's professions, and are willing participants in a co-operative atmosphere."

Q3 Are there any urological diseases today that are much more prominent than they were during your early career? Why is this?

Again, I would say prostate pathology. When I began as a radiologist 20 years ago, the only method of prostate examination was ultrasound. At that time, only 0.5T MRI scanners were available and most MRI examinations were performed in the neurological field. Today, I have so many prostate MRI requests that I do not know how to reduce the waiting list!

Q4 Interdisciplinary collaboration is becoming more and more important throughout medicine. What departments do you work closely with as a urological radiologist and how can collaboration be improved?

Collaborating provides the key to achieve more than one can on their own. It is an opportunity to learn and go beyond your traditional way of thinking. Collaboration occurs when individuals have mutual respect for one another, and one another's professions, and are willing participants in a co-operative atmosphere. I work in a university hospital, and collaboration is implemented for both medical problems and for scientific development. Urological

diseases sit on a wide spectrum of pathology, and therefore interest many specialities, such as urology, surgery, oncology, and radiology. In our hospital, following other institutional experience, we started a prostate cancer unit. Thanks to the interdisciplinary collaboration, we are working towards our aim of reducing waiting times and clarifying the clinical and diagnostic paths of our patients.

Q5 What role do national societies play in the development of young urological radiologists?

Science and knowledge are the foundations of the healthcare profession, and research is one means of achieving these requirements. Young medical doctors are often told what to learn, but the qualified medical doctors are responsible for directing their own learning, and continuous medical education is mandatory. In Europe, participation in continuing medical education programmes is largely voluntary. Many European countries use an hours-based credit system to quantify educational activities. I think that whichever system is adopted, every doctor has a personal responsibility to participate in their own continual professional development.

Q6 Events like the EAU congress share important breakthroughs every year. What results would you like to see from the latest prostate cancer studies?

The goal of all diagnostic techniques is to identify all significant pathologies, while ignoring the insignificant pathologies. I think that radiomic analysis could offer this ability. Therefore, I would like to see more studies in this field because I think that texture analysis is the future of radiology.

Q7 How important is mentorship in modern medical education? Does this extend beyond training into clinical practice?

I think that a good mentor is crucial in every faculty development programme. I had a great mentor. He was always present and patient, and he never tried to intimidate or ridicule me. I remember the good atmosphere when I would review challenging cases under his supervision. Today, I try to transmit the same positive feeling to my residents. I try to teach them that learning is not only about obtaining a good evaluation but is a chance to become a better medical doctor.

Q8 What was the most fascinating case you have been a part of and why?

I remember a patient who underwent abdomen MRI for abnormal alkaline phosphatase levels. I found a little Wirsung duct dilatation. I suggested performing a CT examination, which showed the same feature. No pancreatic lesion was visible! However, the patient's clinical history was not reassuring because he had asthenia. I then performed an endoscopic ultrasound guided pancreatic biopsy, which showed a small adenocarcinoma. I think I saved this patient's life and that is really exciting.

Q9 If you had one piece of advice to give your younger self, what would you say?

I would say to be curious and not be scared of innovations. Every new technology, therapy, and surgical procedure is a new challenge for your amazing job!

"I try to teach them that learning is not only about obtaining a good evaluation but is a chance to become a better medical doctor."

Abstract Reviews

From sacral modulation to the results of the CONTACT study on overactive bladder and benign prostatic hyperplasia, this section captures a snapshot of the crucial action taking place at the EAU's poster presentations.

Association of Super-Extended Lymphadenectomy at Radical Cystectomy with Perioperative Complications and Re-hospitalisation

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Disclosure: The authors have declared no conflict of interest.

Keywords: Bladder cancer, complications, lymphadenectomy, radical cystectomy.

Citation: EMJ Urol. 2019;7[1]:35-36. Abstract Review No. AR1.

The authors performed a retrospective analysis of 284 patients treated with radical cystectomy and lymphadenectomy (LAD) for bladder cancer to assess the differential association of the extent of LAD with perioperative complications and re-hospitalisation. Three LAD templates were defined: limited (lLAD: external, internal, iliac, and obturator), extended (eLAD: up to the crossing of ureter and presacral lymph nodes), and super-extended (sLAD: up to the inferior mesenteric artery). The results showed that sLAD leads to a higher lymph node yield and N2/N3 rate but not to a higher complication rate compared to lLAD and eLAD (all p>0.05).

Current evidence supports the adoption of extended pelvic and iliac lymph node dissection as it identifies more lymph nodes and therefore increases the sensitivity for identification of pathologic lymph node metastasis.[1-3] However, whether the extent of LAD is associated with improved survival is still under debate. Only one randomised trial has been published so far,[4] and it showed no statistical difference in 5-year recurrence-free survival between 433

patients randomised to standard LAD or eLAD. Moreover, as in the authors' study, no difference in complication rates could be observed.

In the past decades, the introduction of novel surgical techniques and improvements in the perioperative management of patients (i.e., enhanced recovery after surgery protocols) have improved perioperative outcomes of patients. However, these have not affected oncologic outcomes or survival.

Bladder cancer is a highly heterogeneous disease. Assessing survival differences considering only the extent of the lymphadenectomy leads inevitably to negative findings. Moreover, the difference in survival in patients treated with standard LAD and eLAD as shown by the current literature, is too small to be assessed in a clinical trial with a reasonable number of patients. The importance of sLAD relies not on disease control and improvement of survival, but much more upon accurate staging. Indeed, with the advent of novel adjuvant systemic therapies, precise nodal staging will play a crucial role in a patient's counselling and clinical decision-making.

References

1. Vazina A et al. Stage specific lymph node metastasis mapping in radical cystectomy specimens. Journal of Urology. 2004;171(5):1830-4.
2. Woldu SL et al. Validating the predictors of outcomes after radical cystectomy for bladder cancer. Cancer. 2019;125(2):223-31.
3. Abdollah F et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. BJU Int. 2012;109(8):1147-54.
4. Gschwend JE et al. Limited versus extended pelvic lymphadenectomy in patients with bladder cancer undergoing radical cystectomy: Survival results from a prospective, randomized trial (LEA AUO AB 25/02). J Clin Oncol. 2016;34(15 Suppl):4503.

Tension-Free Vaginal Tape: Over 10 Years Follow-Up

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Long-term follow-up, mixed urinary incontinence, sling, stress urinary incontinence (SUI) surgery, tension-free vaginal tape (TVT), urinary incontinence.

Citation: EMJ Urol. 2019;7[1]:36-37. Abstract Review No. AR2.

This study set out to examine the long-term outcomes of tension-free vaginal tape (TVT) to treat stress urinary incontinence (SUI) or stress-predominant mixed urinary incontinence (MUI). Women are living longer, which means they live for longer with the effects of any chronic treatments they have had, and thus there is an increasing need to study the long-term outcomes of these treatments. Of particular interest was the evaluation of whether short-term outcomes of TVT could be maintained over a longer period, and a minimum 10-year follow-up was implemented for this. In addition, the researchers were interested in what long-term complications would present, both in terms of anatomic and functional complications, as well as what the larger challenges were for patients over this period.

At a mean follow-up of 139 months, 73% of the cohort was cured; this figure was lower than results in the literature for short and medium-term follow-up, but nonetheless positive. No anatomical complications were encountered, but a statistically significant increase in functional complications was seen: urgency increased from 29.6% to 35.9%, urgency urinary incontinence increased from 31.2% to 34.3%, *de novo* urgency occurred in 6.2% of cases, and *de novo* voiding symptoms appeared in 4.5% of patients.

These results plus data on quality of life show that women who undergo TVT can expect the improvement obtained from their operation to

continue in the long-term. There is, however, an increase in functional complications compared to the short-term. One problem in evaluating results of this kind is that it is difficult to separate a deterioration due to the surgery not lasting over time from symptoms due to new pathologies or simply due to ageing. Studies are needed to enable the identification of bias influencing complications in the long-term.

This is not the first study on the long-term outcomes of TVT,[1-3] but it is the first to include both patients with pure SUI and those with stress-predominant MUI (i.e., SUI+overactive bladder [OAB]). The reason these patients were included in this study is that there are twice as many SUI patients with OAB as without.[4] These results overall are not as positive as the previous studies on pure SUI, but this is explained, at least in part, by the inclusion of patients with SUI+OAB. Studies are needed to compare long-term outcomes of patients with SUI with and without OAB.

References

1. Nilsson CG et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013;24(8):1265-9.
2. Braga A et al. Tension-free vaginal tape for treatment of pure urodynamic stress urinary incontinence: Efficacy and adverse effects at 17-year follow-up. BJU Int. 2018;122(1):113-7.
3. Zhang Y et al. Tension-free vaginal tape for the treatment of stress urinary incontinence: A 13-year prospective follow-up. J Minim Invasive Gynecol. 2018. pii: S1553-4650(18)30425-4.
4. Serati M et al. Urodynamics useless before surgery for female stress urinary incontinence: Are you sure? Results from a multicenter single nation database. Neurourol Urodyn. 2016;35(7):809-12.

A Randomised Controlled Study of the Efficacy of Tadalafil Monotherapy Versus Combination of Tadalafil and Mirabegron for the Treatment of Overactive Bladder Associated with Benign Prostatic Hyperplasia (CONTACT Study)

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Keywords: Benign prostatic hyperplasia (BPH), mirabegron, overactive bladder (OAB), pharmacotherapy, tadarafil.

Citation: EMJ Urol. 2019;7[1]:37-38. Abstract Review No. AR3.

Alpha-1 blockers have been used for the first-line treatment of benign prostatic hyperplasia (BPH).[1] The phosphodiesterase 5 inhibitor tadalafil has recently been used for the treatment of BPH.[2] The combination therapy or add-on of an anticholinergic or β3-adrenoceptor agonist (mirabegron) with α1-blocker is recommended for the treatment of BPH with overactive bladder (OAB).[3] However, the efficacy of add-on treatment of mirabegron with tadalafil has not been reported.

In this study, the authors evaluated the efficacy and safety of the add-on treatment of mirabegron (50 mg/day) for OAB and BPH patients who were not satisfied with tadalafil (5 mg/day) monotherapy for ≥8 weeks. Male BPH patients with remaining OAB symptoms following tadalafil administration for >8 weeks were randomly assigned to either a tadalafil monotherapy (5 mg/day) group (TG) or a tadalafil and

mirabegron combination therapy group (TMG), and were followed for 12 weeks. The primary endpoint was a change from baseline in total overactive bladder symptom score (OABSS). The secondary endpoints were changes in each question of OABSS, international prostate symptom score (IPSS), quality of life index, and micturition chart variables (number of voids per 24 hours, number of urinary urgency episodes per 24 hours, and number of urgency incontinence episodes per 24 hours).

A total of 176 patients were randomised to either TG (87 patients) or TMG (89 patients). The total OABSS (95% confidence interval) of the TMG at 12 weeks was significantly decreased by 1.78 (1.05–2.50) more than that of the TG ($p<0.00001$). Changes in night-time voiding score, urgency score, urgency incontinence score, IPSS total score, IPSS storage subscores, and National Institutes of Health chronic prostatitis symptom index voiding subscores were significantly greater in TMG compared to TG at 4 and 12 weeks after the treatments ($p<0.05$). The change in the number of voids per night, the number of voids per 24 hours, and the number of urgency episodes per 24 hours was significantly reduced in the TMG compared to the TG ($p<0.05$). One severe adverse event (1.2%), pain in the hip joint, was noted in the TG, and seven mild adverse events (8.1%) in the TMG.

In conclusion, the effect of tadalafil and mirabegron combination therapy on relieving OAB symptoms appeared to be greater than that of tadalafil. The present study is the first report on treatment with phosphodiesterase 5 inhibitor and β3 agonist combination regimen.

References

1. Yamanishi T et al. Six-year follow up of silodosin monotherapy for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: What are the factors for continuation or withdrawal? Int J Urol. 2015;22(12):1143-8.
2. Gacci M et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2016;70(1):124-33.
3. Ichihara K et al. A randomized controlled study of the efficacy of tamsulosin monotherapy and its combination with mirabegron for overactive bladder induced by benign prostatic obstruction. J Urol. 2015;193(3):921-6.

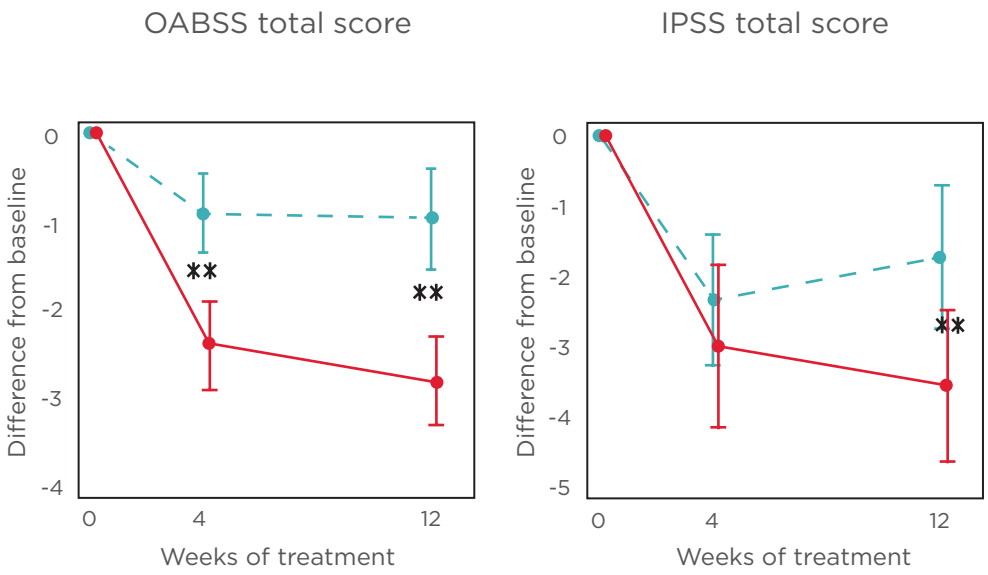

Figure 1: Changes in total overactive bladder symptom score and total international prostate symptom score from baseline to Week 4 and Week 12 of treatment.

Dotted blue line represents the tadalafil monotherapy group and the red line represents the tadalafil and mirabegron combination therapy group.

**p<0.01.

IPPS: international prostate symptom score; OABSS: overactive bladder symptom score.

High Field Single Subject Brain Mapping of Pelvic Floor Motor Control. A 7-Tesla fMRI Study

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Disclosure: The authors have declared no conflicts of interest.

Keywords: 7-Tesla, brain mapping, fMRI, high-field imaging, pelvic floor, single subjects.

Citation: EMJ Urol. 2019;7[1]:39-40. Abstract Review No. AR4.

During poster session 1 of the European Association of Urology (EAU) Congress, Barcelona, Spain, the abstract 'High field single subject brain mapping of pelvic floor motor control. A 7-Tesla fMRI study' was presented. The aim of the study was to further define the brain areas involved in pelvic floor motor control and to indicate whether single-subject mapping of urogenital control is possible using 7-Tesla functional MRI (fMRI). Arguments for the aim of this study are the poorly understood pathophysiology of many functional pelvic floor disorders and its high prevalence. PET, 1.5, and 3-Tesla fMRI studies have already demonstrated brain areas to be involved in pelvic floor motor control, but these studies produced inconsistent findings and only group results have been analysed to date. Firstly, the authors hope to further clarify the brain areas involved in this pelvic floor motor control in healthy volunteers, and, secondly, demonstrate that high-field imaging is a suitable technique to detect urogenital control in these individuals.

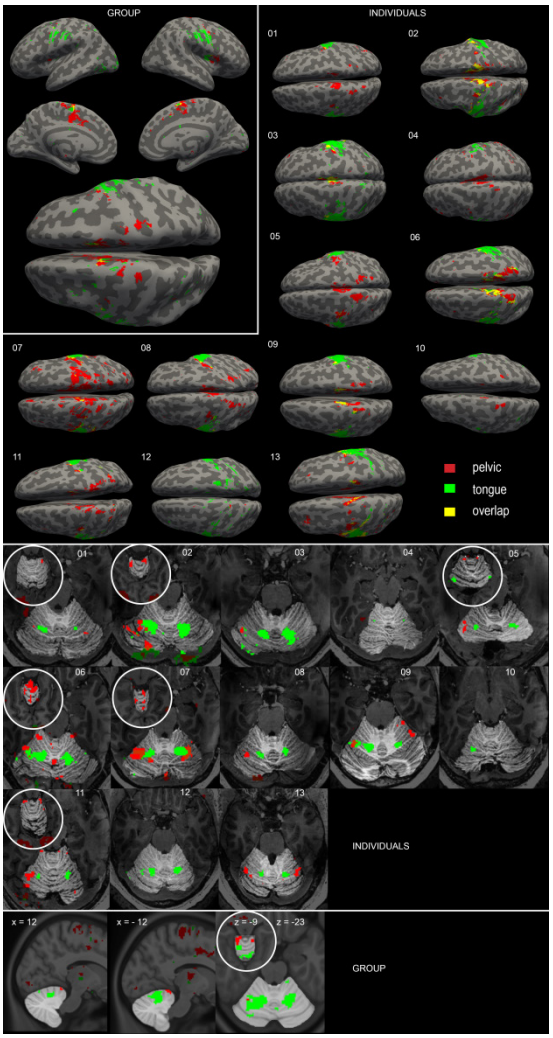

Figure 1: Active clusters found during groups analysis and in individuals of the cortex and the cerebellum.

Seventeen healthy males had undergone a 7-Tesla fMRI (Philips Achieva, Philips, Guildford, UK) performing two tasks: repetitive pelvic floor muscle contractions and, as a control, horizontal tongue movements. Volunteers practised the tasks in the mock scanner. The data from four subjects had to be rejected due to motion artefacts.

During pelvic floor muscle contractions, active clusters were found on the primary motor cortex (M1), supplementary motor area, anterior insula, putamen, thalamus, and cerebellum. Figure 1 shows the results of our group, specifically the individual analyses of both cortex and cerebellar results. In all the subjects, activation of the primary motor cortex was visualised, and when compared to the homunculus the activation is located in the hip

region. In the group analyses the cluster is split in two, whereas in single subjects it appears to be one cluster. In the anterior lobe of the cerebellum, activation during both tasks was objectified in the group analyses. Moreover, these results were also visible in most of the single subjects.

This study demonstrated which brain areas are involved in pelvic floor motor control, and furthermore, showed that the 7-Tesla fMRI is a suitable technique for brain mapping urogenital control in single subjects. Single subject results were comparable and complementary to group results. The discussion following the presentation of this subject mainly focussed on the clinical applicability of this study. This study indicates that the 7-Tesla fMRI might be suitable for demonstrating differences between healthy subjects and patients with pelvic floor disorders and be able to provide information on the pathophysiology of this highly prevalent disease. Other studies using fMRI have shown disease-related changes in activity patterns in patients with urge urinary incontinence.[1] Future perspectives include the clinical potential to use fMRI as a diagnostic tool or to score treatment effects.

References

1. Kutch JJ et al. Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: A MAPP: Research Network Neuroimaging Study. Neuroimage Clin. 2015;8:493-502.

Sacral Neuromodulation: A Comparison of Office-Based Test Stimulation versus Staged Implant

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Office-based test stimulation, refractory voiding dysfunction, sacral neuromodulation, staged technique, stimulation testing/trial phase, tined lead.

Citation: EMJ Urol. 2019;7[1]:40-41. Abstract Review No. AR5.

INTRODUCTION AND OBJECTIVES

Sacral neuromodulation is commonly used as a third-line treatment option in patients with a refractory voiding dysfunction, such as overactive bladder, non-obstructive urinary retention, urgency-frequency syndrome, or urge urinary incontinence.[1] The process for the possible placement of the device is divided into two phases. First is the testing or trial phase, which has the objective of determining the perception and response of the patient to the stimulation, assessing improvement during 1–2 weeks.[2,3] Then, those who have a successful trial continue to the placement of the implantable pulse generator (IPG) in the operating room (OR). For the trial phase, two different modalities can be performed. The first is the office-based test stimulation (OTS), an inexpensive and minimally invasive procedure performed in the office under a local anaesthesic.[4] However, the rate of lead displacement or migration was considered to be an issue; thus, a staged technique was developed, consisting of an initial placement of a tined-lead in the OR under sedation.[5] Besides the risk of lead migration in the OTS group, it is also considered to have a lower success rate. Nevertheless, the studies are limited and focus on special populations.[4] The authors considered whether the rate of success of the stimulation trial was higher actually when the first stage was

performed in the OR, and if there were any other variables that could have a predictive role for trial success.

METHODS

The study began by retrospectively querying a cohort of patients in the authors' institution who had sacral neuromodulation testing from 2003–2016. Recordings were taken of baseline characteristics, urodynamic study results, lower urinary tract symptoms, and other treatments received for voiding dysfunction at each visit. Testing modality, OR report, and postoperative evaluations were reviewed. The authors then described categorical baseline variables with percentages and continuous normally distributed variables with means. Patients who had ≥50% symptom improvement after stimulation trial were defined as responders and went on to have IPG placement. In this analysis, responders or non-responders served as a dichotomous categorical dependent variable, while multiple independent variables were analysed using multivariable logistic regressions. The study found odds ratio with 95% confidence intervals estimating the probability of being responder based on multiple predictor variables.

RESULTS

From the final cohort of 103 patients, 88 (85.4%) met the improvement criteria to progress to IPG placement. In the OTS group, 40 of the 51 (78.0%) patients had a successful trial (mean trial duration of 7.4 days); 82.0% of these were tested with bilateral wires; 9 of 51 had equivocal results, lead displacement, or migration, and underwent tined-lead placement in OR, all progressing to IPG placement. In the staged group, 39 of 52 (75.0%) had a successful trial (mean trial duration of 9.1 days). Overall, no significant differences were noted for primary lower urinary tract symptoms, urodynamic study parameters, previous treatments, or other baseline variables in predicting implantation success between the two techniques after performing multivariable logistic regression.

DISCUSSION AND CONCLUSIONS

OTS had an equivalent success rate compared with the staged procedure. Patients who had successful initial OTS received one less anaesthetic. They generally had two wires placed, thus allowing assessment for improvement at two different locations. OTS has advantages of cost-effectiveness and the ability to trial at more than one site while achieving similar success rates, and should be considered the procedure of choice in experienced hands. A next step in this study could be the long-term follow-up of this cohort to assess outcomes and analyse differences between the groups.

References

1. Williams ER, Siegel SW. Procedural techniques in sacral nerve modulation. Int Urogynecol J. 2010;21(2):S453-60.
2. Kacker R, Das AK. Selection of ideal candidates for neuromodulation in refractory overactive bladder. Curr Urol Rep. 2010;11(6):372-8.
3. Abello A, Das AK. Electrical neuromodulation in the management of lower urinary tract dysfunction: Evidence, experience and future prospects. Ther Adv Urol. 2018;10(5):165-73.
4. Borawski KM et al. Predicting implantation with a neuromodulator using two different test stimulation techniques: A prospective randomized study in urge incontinent women. Neurourol Urodyn. 2007;26(1):14-8.
5. Leong RK et al. PNE versus 1st stage tined lead procedure: A direct comparison to select the most sensitive test method to identify patients suitable for sacral neuromodulation therapy. Neurourol Urodyn. 2011;30(7):1249-52.

A New Global Voice for People Affected by Bladder Cancer

Feature from the European Association of Urology (EAU) Congress in Barcelona, Spain

World Bladder Cancer Patient Coalition

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Citation: EMJ Urol. 2019;7[1]:42-43.

For the first time ever, people affected by bladder cancer now have a global voice. The World Bladder Cancer Patient Coalition was officially launched on Monday 18th March 2019 at the European Association of Urology (EAU) Congress in Barcelona, Spain.

Approximately 430,000 people are diagnosed with invasive bladder cancer around the world each year.[1] Globally, there are 2.7 million people who are currently living with bladder cancer.[2] In the Western world, bladder cancer is the fourth most common malignancy in men and the eighth most common in women.[3] About 1 in 25 Western men and 1 in 80 Western women will be diagnosed with bladder cancer at some point in their lives.[2] Women are 23% more likely to die from the disease compared to men with bladder cancer.[4]

The Bladder Cancer Advocacy Network (USA), Fight Bladder Cancer (UK), and Bladder Cancer Canada worked together to establish the World Bladder Cancer Patient Coalition. Action Bladder Cancer UK, BladderCancer.org.au Australia, Blaerekreftforeningen Norway, Les Zuros France, and PaLiNUro Italy participated in the inaugural meeting and were invited to become full members. Other patient advocates, health professionals, academics, policy-makers, researchers, and representatives from the pharmaceutical and medical device industries also attended the launch.

Piyush Agarwal, Center for Cancer Research (U.S.) National Cancer Institute, Bethesda, Maryland, USA, spoke at the launch event. He said: "The World Bladder Cancer Patient Coalition unites patients around the world, giving them a powerful voice in the fight against a lethal disease that significantly impacts not only their survival but also their quality of life. The World Bladder Cancer Patient Coalition aims to create a global voice that hopes to alleviate much of the pain and suffering associated with bladder cancer."

"Treatment, research, and support for bladder cancer patients varies widely across the globe and even within countries," said Ken Bagshaw, bladder cancer patient and interim President of the World Bladder Cancer Patient Coalition. "It's critical that we mobilise bladder cancer patient organisations across the world to help ensure the best possible outcomes for patients."

The World Bladder Cancer Patient Coalition is governed by a board of directors. This board is composed of people diagnosed with bladder cancer, carers of bladder cancer patients, and those engaged with bladder cancer organisations at the national level.[5]

The missions of the World Bladder Cancer Patient Coalition are to:

- Foster an international community of people affected by bladder cancer.
- Advocate for access to the best possible bladder cancer information, support, and care.
- Build alliances with health professionals, policy makers, academics, researchers, and industry.

In its first year of operation, the organisation will focus on Bladder Cancer Awareness Month in May, producing a regular newsletter for stakeholders, and developing a toolkit to help establish and build national bladder cancer patient organisations.

The World Bladder Cancer Patient Coalition welcomes other bladder cancer patient organisations to apply for membership. To be eligible for full membership, organisations must be (a) supporting or rendering services exclusively to bladder cancer patients and their caregivers; and/or (b) raising bladder cancer awareness, promoting bladder cancer research, and empowering organisations that support or render services to bladder cancer patients and their caregivers; and (c) a bladder cancer patient organisation.

References

1. Ferlay J et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Ploeg M et al. The present and future burden of urinary bladder cancer in the world. World J Urol. 2009;27(3):289-93.
3. Kirkali Z et al. Bladder cancer: Epidemiology, staging and grading, and diagnosis. Urology. 2005;66(6): 4-34.
4. Uhlig A et al. Gender Specific Differences in Disease-Free, Cancer Specific and Overall Survival after Radical Cystectomy for Bladder Cancer: A Systematic Review and Meta-Analysis. J Urol. 2018;200(1): 48-60.
5. World Bladder Cancer Patient Coalition. World Bladder Cancer Patient Coalition website. Available at: www.worldbladdercancer.org. Last accessed: 18 March 2019.

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The Efficacy and Safety of Flexible Ureterorenoscopy in Treatment of Kidney Stones >2 cm: A Review of the Literature

EDITOR'S PICK

There is limited data on the efficacy and safety of using flexible ureterorenoscopy (fURS) in kidney stones >2 cm in size. Robotic surgery is increasingly being applied mostly in abdominal uro-oncologic procedures, including prostate cancer, kidney cancer, and bladder cancer. Recently, a robotic system has been introduced for the surgical management of particularly large kidney stones.[1] This robotic system is called Avicenna Roboflex™ and its components include a surgeon's console and manipulator of the fURS. The console with the joystick enables the deflection, rotation, advancing, and retracting of the instrument. The speed of movements can be regulated. This new promising technology might be useful particularly in the minimally invasive surgical management of large kidney stones, as it supplies a confortable sitting position for the operating surgeon, enables delicate movements of the fURS, and exposes the surgeon to less radiation because it has a longer distance between the console and the patient due to the C-radiation-arm.[1]

Reference

1. Rassweiler J et al. Robot-assisted flexible ureteroscopy: An update. Urolithiasis. 2018;46(1):69-77.

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Keywords: Flexible ureterorenoscopy (fURS), percutaneous nephrolithotomy (PNL), urinary tract stone disease.

Citation: EMJ Urol. 2019;7[1]:46-50.

Abstract

With the advancement of technology, flexible ureterorenoscopy (fURS) has gained popularity among urologists, and fURS is widely accepted as an alternative to extracorporeal shockwave lithotripsy and percutaneous nephrolithotomy. Recent technological and surgical innovations have promoted less invasive treatment options, such as fURS. The use of fibre optics in imaging, an

increased deflection capability, and more appropriate dimensions of the device have increased the efficiency of fURS in stone disease treatment. However, there are limited data evaluating the efficacy of fURS in kidney stones >2 cm. Thus, in this review article, the authors assess the efficacy and complications of fURS for the treatment of kidney stones >2 cm.

INTRODUCTION

Urinary tract stone disease has a high rate of morbidity throughout the world and is one of the most common urological diseases, with an incidence rate of 10–15%.[1] This has encouraged the development of treatment options that are minimally invasive and highly effective for the treatment of urolithiasis. With the urological field moving away from open surgery, recent technological and surgical innovations have promoted less invasive interventions, such as percutaneous nephrolithotomy (PNL), flexible ureterorenoscopy (fURS), and extracorporeal shock wave lithotripsy (ESWL).[2] Following the first PNL applications of Fernström and Johnson in the 1970s,[3] this procedure was used with instruments with smaller calibrations with the aim of reducing complication and morbidity rates without decreasing the stone-free rate.[3-4] Thus with a smaller diameter entry tract, a reduction has been achieved in complications, such as renal parenchyma damage and blood loss.[5-6]

Technical advances in fURS since the 1980s, including the use of fibre optics in imaging and light transmission, the more appropriate dimensions of the device and the increased deflection capability have increased the efficiency of this technique for stone disease treatment.[7] Furthermore, higher stone-free rates have been reported in comparison with ESWL and lower morbidity rates than PNL.[8]

The surgical method to be selected in kidney stone treatment depends primarily on stone size and localisation. In treatment algorithms and guidelines, while PNL is recommended as the first choice in kidney stones >2 cm, ESWL or endourology (fURS and PNL) are recommended for stones 1–2 cm in size, and ESWL or fURS for stones <1 cm. fURS is not recommended as the first treatment choice because of the low stone-free rate of stones >2 cm and the need for repeated fURS sessions.[9] However, for patients with bleeding disorders, obesity, or a renal congenital anomaly, fURS is recommended as an alternative treatment option to PNL.[10] Recently, fURS has been used by urologists for the treatment of stones >2 cm, as the rate and degree of complications are lower than in PNL and stone-free rates are comparable.[11]

The authors searched PubMed for the articles that investigated fURS in the treatment of renal stones >2 cm with the aim to evaluate the efficacy of fURS treatment for kidney stones >2 cm in size.

DISCUSSION

With the development of anterograde and retrograde techniques in nephrolithiasis treatment, the type of PNL treatment was defined according to the dimensions of the instruments used in the procedure: mini-PNL (14–20 Ch access diameter) was defined in 1998,[4] micro-PNL (4.8 Ch) in 2011,[12] and ultra-mini PNL (11–13 Ch) in 2013.[13] Despite the high stone-free rates obtained, standard PNL is more invasive than other treatment methods.[14] It has been reported in the literature that PNL should be the primary selected surgical technique for the treatment of large renal stones (>2 cm), with stone-free rates of 85–95% after a single session.[15] However, this has also entailed serious complications, including bleeding requiring blood transfusion (11.2–17.5%), fever (21.0–32.1%), pneumothorax (0.0–4.0%), colon injury (<1.0%), and sepsis (0.25-1.5%).[16] In addition, the anaesthesia risk is further increased during PNL because the patient is placed in a prone position and can experience contractions of extremities and a difficult airway.[16] The risks caused by the prone position in obese patients or those with cardiopulmonary disease, including the negative effects on haemodynamics and the risk of muscle-nerve damage, have led to current application of PNL in the supine position.[17,18] However, the prone position is more widely used because the urologist may not be familiar with the supine position and the prone position allows a wider access area.[19]

The complication rates and severity in fURS are less worrying for both the surgeon and the patient. Possible complications have been reported as haemorrhage, intrapelvic or subcapsular haematoma, ureteral perforation, avulsion, and mucosal injury. The postoperative complication rates in the literature have been reported as 3–4%, and the majority of these have been determined as Clavien Grade 1–2.[20]

Another complication of concern to urologists is the development of sepsis associated with increased pyelovenous and pyelolymphatic passage due to increased intrarenal pressure because of the irrigation fluid used during fURS. Intrarenal pressure is the most important factor for infectious complications.[21] In the Clinical Research Office of the Endourological Society (CROES) ureteroscopy global study, postoperative infectious complications were reported in 2.97% of cases, of which 0.30% represented severe sepsis.[22] In a randomised, prospective study by Güzelburç et al.,[23] ethanol was added to the irrigation fluid in patients with renal stones >2 cm and fluid elimination was compared by measuring the ethanol level in the blood at certain intervals. The results showed no statistically significant difference between the different techniques in terms of irrigation fluid absorption (fURS: 20–573 mL; PNL: 13–364 mL). The prolonged operating time and increased amount of irrigation fluid used was not reported to have affected fluid absorption in the fURS group, but absorption was increased in the PNL group. Manual application of the water force in fURS is an important factor in increasing intrarenal pressure, while the access sheath is the most effective factor in maintaining low pressure. Intrarenal pressure can be kept low with the vacuum mechanism in mini-PNL but cannot be controlled in micro and ultra-mini-PNL.[24]

Mini-PNL and fURS are minimally invasive approaches that are effectively applied in the treatment of renal stones, but there is no definitive data in the literature showing that either of these techniques are a good alternative to standard PNL.[25] Mini-PNL, which started to be used at the end of the 1990s, has not been determined to make a difference in stone-free rates compared to standard PNL, but a decrease in nephron loss and serious postoperative complication has been attributed to the technique.[26, 27] When the dimension of the entry tract to the renal pelvis is reduced, the risk of bleeding and need for blood transfusion is reduced compared to standard PNL.[28] However, when the literature is examined, studies demonstrate that fURS provides lower complications and higher efficacy than mini-PNL.[29,30] Zeng et al.[31] compared results in patients with renal stones >2 cm following mini-PNL or fURS, finding no difference between the two groups regarding the fall in haemoglobin level, the need for blood transfusion, complication rates, fever, and sepsis. However, the stone-free rate was found to be higher in the patients treated with mini-PNL in a single session compared to those treated with fURS (PNL: 71.70% versus fURS: 43.40%).

Generally, the results of PNL and fURS techniques evaluated in the literature have been associated with a greater preference for PNL if renal stones are >2 cm. In a multicentre study by Hyams et al.,[32] fURS was performed for patients with renal stones 2–3 cm in size and stone-free rate was 66% when clinically insignificant residual fragment size was accepted as <2 mm. When clinically insignificant residual fragment size was accepted as <4 mm, the stone-free rate was 83%, 16% of the patients needed a second intervention, and one patient had ureteral perforation. Based on these data, it was therefore concluded that fURS was an effective method for the treatment of renal stones 2–3 cm in size which could be applied less invasively and with lower costs in selected patients.[32]

In a study from 2009, the outcomes of 22 patients, with a mean stone size of 3 cm who were treated with fURS were analysed. The average number of interventions per patient was reported as 1.82, the general stone-free rate as 90.9%, and mean operating time as 72 minutes (range: 28–138 minutes). Two interventions were required in 63% of patients, and three interventions in 5%. The authors reported that, with technological advances, fURS could be an alternative treatment for large renal stones.[33] In a series of 167 patients with large stones ≥2 cm, Scotland et al.[34] reported that the mean number of interventions per patient was 1.65, and the general stone-free rate was 59.4% after a single procedure, 90.2% when two procedures were completed, and 94% after three procedures. In the evaluation of subgroups, comparisons were made between those with stones of 2.0–2.9 cm and those with stones ≥3.0 cm. In the first group, there was a

lower need for >1 intervention, and stone size was reported to be the most important predictor of a staged procedure and stone-free rates. However, a shorter length of stay in hospital and lower costs were reported as advantages of ureterorenoscopy. In another study that compared the costs of fURS and PNL applied to patients with renal stones of 2–3 cm, the mean number of interventions per patient was reported as 1.6 for PNL and 1.1 for fURS, and the costs were found to be lower for fURS.[35]

A study by Pan et al.[36] compared the clinical outcome and the cost-effectiveness of between fURS and mini-PCNL for the management of single renal stone of 2–3 cm. Although the costs of hospitalisation and laboratory and radiology tests were initially reported to be lower in fURS, in respect of total medical costs with additional interventions, visits and general hospital stay, there was no significant difference between the groups, but the mean number of interventions (± standard error of the mean) was determined to be lower in PNL (1.03±0.20 versus 1.18±0.40 for fURS).

A meta-analysis examined 12 studies evaluating the results of 651 patients applied with fURS for renal stones >2 cm. The mean number of interventions was found to be 1.45, the stone-free rate 91.0% (range: 77.0–97.5%) and the complication rate was determined as 4.5%. In the subgroup analysis of patients with stones of 2–3 cm and >3 cm, the success rate was higher in the 2–3 cm stone size group compared to the >3 cm group (93.0% versus 76.8%); the major complication rate (0.0% versus 10.0%) and the number of interventions (1.39±0.18 versus 1.85±0.02) were determined to be lower in the 2–3 cm stone size group compared with the >3 cm group.[37]

In a series of 143 patients, Karakoç et al.[38] compared the data of 86 PNL patients to 57 fURS patients. It was reported that the mean operating time was statistically significantly longer in fURS (PNL: 75.55±21.5 minutes versus fURS: 100.26±33.26 minutes; p<0.001). In the same study, all complications were seen more frequently in the PNL group: 2 patients required blood transfusion and 9 patients developed fever, whereas no patients required blood transfusion or developed fever in the fURS group. The mean length of hospital stay was shown to be statistically significantly shorter in the fURS group (fURS: 1.56±0.80 days versus PNL: 4.57±2.10 days; p<0.001). The stone-free rates were reported as 66.6% after the first session and 87.7% after the second in the fURS group and as 91.8% in a single session in the PNL group.

In a study that examined the data of 116 patients with a solitary kidney and renal stone of >2 cm, PNL was used in 60 patients and fURS in 56 patients.[39] The mean operating time (±standard deviation) in the fURS group was found to be statistically significantly shorter than that of the PNL group (fURS: 99.46±31.08 minutes versus PNL: 78.95±29.81 minutes; p<0.001). The mean (± standard deviation) length of hospital stay was determined to be statistically significantly longer in the PNL group (PNL: 5.9±1.5 days versus fURS: 2.0±1.0 days; p<0.001). At the end of a 3-month follow-up period, the general stone-free rate was reported to be 83.3% for PNL and 82.1% for fURS, with no statistically significant difference determined. Although general complications and the fall in haemoglobin were determined to be significantly higher in the PNL group (p=0.04), there was no requirement for blood transfusion in either group and no significant increase in postoperative creatinine levels. The authors concluded that with low complications and high efficacy, fURS could be selected as an alternative to PNL in patients with a solitary kidney and stone of >2 cm.[39]

CONCLUSION

In patients with renal stones of >2 cm, the stone-free rates obtained with staged interventions are comparable with those of PNL. Taking complications and stone-free rates into consideration for patients who are planned to undergo surgery for large renal stones, it seems that fURS could be applied effectively in selected patients. However, prior to fURS, patients should be informed that >1 intervention may be necessary. Finally, fURS can be safely applied to patients who are at high risk for PNL.

A REPORT OF A SPECIAL EAU SESSION RELATED TO A PROBLEMATIC CASE OF FURS ←

References

1. Sorokin I et al. Epidemiology of stone disease across the world. World J Urol. 2017;35(9):1301-20.
2. Desai M et al. Treatment selection for urolithiasis: Percutaneous nephrolithotomy, ureteroscopy, shock wave lithotripsy, and active monitoring. World J Urol. 2017;35(9):1395-7.
3. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol. 1976;10(3):257-9.
4. Jackman SV et al. The "mini perc" technique: A less invasive alternative to percutaneous nephrolithotomy. World J Urol. 1998;16(6):371-4.
5. Kukreja R et al. Factors affecting blood loss during percutaneous nephrolithotomy: Prospective study. J Endourol. 2004;18(8):715-22.
6. Emiliani E et al. Renal parenchyma injury after percutaneous nephrolithotomy tract dilatations in pig and cadaveric kidney models. Cent European J Urol. 2017;70(1):69-75.
7. Doizi S, Traxer O. Flexible ureteroscopy: Technique, tips and tricks. Urolithiasis. 2018;46(1):47-58.
8. Kim TJ et al. Analysis of factors affecting re-admission after retrograde intrarenal surgery for renal stone. World J Urol. 2018;36:1-6.
9. European Association of Urology. EAU Guidelines on Urolithiasis. 2018. Available at: http://uroweb.org/guideline/urolithiasis/. Last accessed: 6 March 2019.
10. Al-Qahtani SM et al. Predictors of clinical outcomes of flexible ureterorenoscopy with holmium laser for renal stone greater than 2 cm. Adv Urol. 2012;534-47.
11. El Hamed AMA et al. Single session vs two sessions of flexible ureterosopy (FURS) for dusting of renal pelvic stones 2-3 cm in diameter: Does stone size or hardness play a role in number of sessions to be applied? Turk J Urol. 2017;43(2):158-61.
12. Bader MJ et al. The "all-seeing needle": Initial results of an optical puncture system confirming access in percutaneous nephrolithotomy. Eur Urol. 2011;59(6):1054-9.
13. Desai J, Solanki R. Ultra-mini percutaneous nephrolithotomy (UMP): One more armamentarium. BJU Int. 2013;112(7):1046-9.
14. Zhu W et al. Minimally invasive versus standard percutaneous nephrolithotomy: A meta-analysis. Urolithiasis. 2015;43(6):563-70.
15. Bryniarski P et al. A randomized controlled study to analyze the safety and efficacy of percutaneous nephrolithotripsy and retrograde intrarenal surgery in the management of renal stones more than 2 cm in diameter. J Endourol. 2012;26(1):52-7.
16. Koyuncu H et al. Intrarenal surgery vs percutaneous nephrolithotomy in the management of lower pole stones greater than 2 cm. Int Braz J Urol. 2015;41(2):245-51.
17. de la Rosette JJ et al. Beyond prone position in percutaneous nephrolithotomy: A comprehensive review. Eur Urol. 2008;54(6):1262-9.
18. Basiri A, Mohammadi Sichani M. Supine percutaneous nephrolithotomy, is it really effective? A systematic review of literature. Urol J. 2009;6(2):73-7.
19. Armitage J et al. Percutaneous nephrolithotomy in the United Kingdom: Results of a prospective data registry. Eur Urol. 2012;61(6):1188-93.
20. van Cleynenbreugel B et al. Retrograde intrarenal surgery for renal stones - Part 1. Turk J Urol. 2017;43(2):112-21.
21. Osther PJ. Risks of flexible ureterorenoscopy: Pathophysiology and prevention. Urolithiasis. 2018;46(1):59-67.
22. Somani BK et al. Complications associated with ureterorenoscopy (URS) related to treatment of urolithiasis: The clinical research office of Endourological Society URS Global study. World J Urol. 2017;35(4):675-1.
23. Güzelburç V et al. Comparison of absorbed irrigation fluid volumes during retrograde intrarenal surgery and percutaneous nephrolithotomy for the treatment of kidney stones larger than 2 cm. SpringerPlus. 2016;5(1):1707.
24. Tokas T et al. Pressure matters 2: Intrarenal pressure ranges during upper-tract endourological procedures. World J Urol. 2019;37(1):133-42.
25. Jiang H et al. Minimally invasive percutaneous nephrolithotomy versus retrograde intrarenal surgery for upper urinary stones: A systematic review and metaanalysis. Biomed Res Int. 2017. Article ID: 2035851.
26. Zhu W et al. Minimally invasive versus standard percutaneous nephrolithotomy: A meta-analysis Urolithiasis. 2015;43(6):563-70.
27. Druskin SC, Ziemba JB. Minimally invasive ('Mini') percutaneous nephrolithotomy: Classification, indications, and outcomes. Curr Urol Rep. 2016;17(4):30.
28. Sun H et al. Safety and efficacy of minimally invasive percutaneous nephrolithotomy in the treatment of patients with medullary sponge kidney. Urolithiasis. 2016;44(5):421-6.
29. Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. BJU Int. 2006;98(6):1283-8.
30. Aboumarzouk OM et al. Flexible ureteroscopy and laser lithotripsy for stones >2 cm: A systematic review and meta-analysis. J Endourol. 2012;26(10):1257-63.
31. Zeng G et al. The comparison of minimally invasive percutaneous nephrolithotomy and retrograde intrarenal surgery for stones larger than 2 cm in patients with a solitary kidney: A matched-pair analysis. World J Urol. 2014;33(8):1159-64.
32. Hyams ES et al. Flexible ureterorenoscopy and holmium laser lithotripsy for the management of renal stone burdens that measure 2 to 3 cm: A multi-institutional experience. J Endourol. 2010;24(10):1583-8.
33. Riley JM et al. Retrograde ureteroscopy for renal stones larger than 2.5 cm. J Endourol. 2009;23(9):1395-8.
34. Scotland KB et al. Retrograde ureteroscopic management of large renal calculi: A single institutional experience and concise literature review. J Endourol. 2018;32(7):601-7.
35. Hyams ES, Shah O. Percutaneous nephrostolithotomy versus flexible ureteroscopy/holmium laser lithotripsy: Cost and outcome analysis. J Urol. 2009;182(3):1012-7.
36. Pan J et al. fURS versus mPNL for single renal stone of 2–3 cm: Clinical outcome and cost-effective analysis in Chinese medical setting. Urolithiasis. 2013;41(1):73-8.
37. Geraghty R et al. Evidence for ureterorenoscopy and laser fragmentation (URSL) for large renal stones in the modern era. Curr Urol Rep. 2015;16(8):54-9.
38. Karakoc O et al. Comparison of retrograde intrarenal surgery and percutaneous nephrolithotomy for the treatment of renal stones greater than 2cm. Turk J Urol. 2015;41(2):73-7.
39. Bai Y et al. Percutaneous nephrolithotomy versus retrograde intrarenal surgery for the treatment of kidney stones up to 2 cm in patients with solitary kidney: A single centre experience. BMC Urol. 2017;17(1):9.

Immunotherapy in Prostate Cancer: Recent Advances and Future Directions

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Abstract

In recent years, immunotherapy has been proposed for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (PCa). Clinical trials using Sipuleucel-T have demonstrated a survival benefit in PCa patients, suggesting that this cancer is linked to a limited immune response. However, the outcome of PCa treated with immune therapeutics has limited benefits in monotherapy: novel vaccination approaches and immune checkpoint blockade gave disappointing results. Several combinations of therapies, such as novel cancer vaccines or checkpoint inhibitors with different immunotherapeutic agents, combined with hormone therapy (enzalutamide, abiraterone acetate), radiotherapy or radium-223, DNA-damaging agents (olaparib), or chemotherapy (docetaxel) hold great promise for eliciting an immune response and improving clinical outcomes in PCa. The goal of immunotherapy is to overcome immunosuppression and destroy cancer cells, or at least to induce those pathways that go back from 'the escape phase to equilibrium phase' according to the definition of cancer immunoediting. The aim of this review is to analyse the immune responses during PCa progression and to present the current data regarding immune therapies for PCa.

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy diagnosed and the second most common cause of cancer-related death among men worldwide.[1] Androgen deprivation therapy (ADT) is the primary therapeutic approach, but, despite the high rate of progression-free survival

(PFS), 30–50% of patients progress to castration-resistant prostate cancer (CRPC), detected by the rising of prostate specific antigen (PSA) values in the blood.[2]

CRPC presents a spectrum of diseases, ranging from the asymptomatic form without evidence of metastasis, to the advanced form with multiple distant metastases (mCRPC) and with a poor prognosis. CRPC is characterised by hyper-activation and/or over-expression of the androgen receptor (AR) resulting in the transcription of downstream target genes and consequent tumour progression, notwith standing the presence of castrate levels of circulating testosterone in patients.[3] mCRPC patients are currently treated with chemotherapeutic drugs, such as docetaxel and cabazitaxel, or with the new generation of anti-androgens, enzalutamide and abiraterone acetate, which target AR activation either directly or indirectly.[2] In 2013, radium-223 dichloride was U.S. Food and Drug Administration (FDA)-approved for the reduction of bone metastases.[4] Targeting the immune system represents an important tool for patients with this form of disease and combined therapies with multiple immunotherapies or with immunotherapy and conventional compounds are currently under evaluation.

There is a continuous crosstalk between tumour cells and the immune system during cancer progression; an anti-tumour immune response is activated both by local tissue damage and by mutated proteins expressed by cancer cells. On the other hand, tumour microenvironment alters myeloid and lymphoid cells, facilitating the progressive suppression of the host immune response.[5,6]

Several studies show that the adaptive immune system recognises PCa tumour-associated antigens (TAA), as demonstrated by the presence of tumour infiltrating lymphocytes (TIL) and auto-antibodies to prostate-specific proteins in the peripheral blood of patients.[7] A high amount of TIL has often been correlated with longer patient survival, whereas a decrease in TIL was detected in high grade prostatic adenocarcinomas compared to benign nodular prostatic hyperplasia.[8] Certain immunosuppressive phenotypes are associated with a moderate recognition of PCa antigens, which drives tumour progression. Moreover, M2-polarised tumour-associated macrophages (TAM) represent a significant component of PCa inflammatory infiltrate, and a high density of TAM is observed in both epithelial and stromal compartments of tumour tissue and is statistically associated with poorer prognosis.[9] Increased number of TAM in PCa biopsy is predictive of worse recurrence free survival in men treated with primary ADT. Regulatory T cells (Tregs) and/or myeloid-derived suppressor cells are also increased in the tumour tissue and peripheral blood of PCa patients, and this feature correlates with other negative prognostic factors, such as lactate dehydrogenase, alkaline phosphatase, PSA, and anaemia.[10] Finally, a strong correlation between the presence of dendritic cells (DC) and PCa prognosis has been reported, since metastatic patients show fewer circulating myeloid DC than their age-matched controls and a lower number of DC correlates with a higher Gleason score, while DC are elevated in low risk cancer.[11] The recruitment of mesenchymal stem cells also supports an immunosuppressive microenvironment,[12] as well as elevated levels of indoleamine 2, 3-dioxygenase, nitric oxide, IL-2, prostaglandin E2, transforming growth factor-β, arginase, and adenosine.[6]

The goal of immunotherapy is to overcome the immunosuppressive microenvironment and to stimulate an immune response against tumour cells to improve patient outcomes. On the other hand, it is important to evaluate how much the immunological system is compromised when considering the most appropriate immunotherapy.[13] Herein, the authors analyse the different approaches of immunotherapy for PCa, used both as a single-agent or in combination. Table 1 contains a list of the ongoing studies mentioned in this article.

CANCER VACCINES

The goal of cancer vaccines is to induce the immune system to recognise TAA and to elicit a T cell response aimed at reducing tumour mass and protecting against tumour recurrence or metastatic disease. Some prostate-specific antigens, like PSA, prostate specific membrane antigen (PSMA), or prostatic acid phosphatase (PAP), are targets of several antitumour vaccines.

Table 1: Summary of mentioned ongoing clinical trials in prostate cancer.

Therapy	Molecule	Mechanism of action	Trial Phase	Trial Identifier
Sipuleucel-T (Provenge®)	Autologous cellular immunotherapy	Activates an antitumor response against PAP	Phase II Phase II	NCT01804465[14] NCT02463799[15]
DCVAC/PCa	Autologous Poly I:C activated DC loaded with killed LNCaP cells	Evocation of immune response	Phase III	NCT02111577[16]
PROSTVAC-VF	Viral based vaccine target PSA	Promotes an immune response against PSA-expressing cells	Phase II Phase II Phase I/II Phase II Phase II	NCT02326805[17] NCT02506114[18] NCT02933255[19] NCT02649855[20] NCT01875250 [21]
ADXS31-142	Live attenuated *Listeria monocytogenes*	Recruitment of CD4+ and CD8+ cells	Phase I/II	NCT02325557[22]
ProstAtak	Viral cancer vaccine	T cell activation and IL-2 production	Phase III	NCT01436968[23]
Ipilimumab (Yervoy®)	IgG1 human monoclonal antibody	Binds and locks the activity of CTLA-4	Phase I Phase I	NCT02601014[24] NCT01804465[14]
Nivolumab (Opdivo®)	IgG4 human monoclonal antibody	Prevents the binding of PD-1 to its ligands PD-L1 and PD-L2	Phase I	NCT02601014[24]
Pembrolizumab	IgG4 humanised monoclonal antibody	Blocks PD-1	Phase I/II Phase I/II Phase II Phase II	NCT02325557[22] NCT02861573[25] NCT02312557[26] NCT03093428[27]
Durvalumab	IgG1κ human monoclonal antibody	Blocks PD-L1	Phase I/II	NCT02484404[28]
Tremelimumab	IgG2 human monoclonal antibody	Blocks the inhibitory signal resulting from CTLA-4 activity	Phase II	NCT03204812[29]
Atezolizumab	IgG1 humanised monoclonal antibody	Blocks PD-L1	Phase II Phase II	NCT03016312[30] NCT02814669[31]
CAR T cells therapy	Chimeric antigen receptor T cells	Engineered patient's T cells modified to recognise and destroy tumour cells	Phase I	NCT01140373[32]

Antigen-loaded DC, as well as synthetic peptides, manipulated tumour cells, and viral vectors, are some vaccination strategies used to improve the prognosis and quality of life of patients with advanced or recurrent PCa.[33]

Sipuleucel-T

Sipuleucel-T (Provenge®) is an autologous cell-based immunotherapy for the treatment of asymptomatic or minimally symptomatic mCRPC and it remains the only FDA-approved vaccine for PCa.[34] This vaccine activates an antitumour immune response against PAP, a secreted glycoprotein synthesised in prostate epithelium, usually increased during cancer progression.[35] This personalised immunotherapy is the result of immune cells harvested from the patient via leukapheresis and incubated with a recombinant fusion protein (PA2024) consisting of PAP and granulocyte-macrophage colony-stimulating factor (GM-CSF), to stimulate antigen-

presenting cells and to obtain mature DC. Sipuleucel-T is then reinfused into the patient to evoke an antitumour immune response against PCa cells expressing PAP. After three cycles over 4 weeks, patients develop an appreciable specific T cell activation and production of antibodies against the fusion protein.[36] Three randomised Phase III clinical trials were completed and all showed a delay in disease related pain.[7,17,18] Sipuleucel-T is generally well tolerated, with only few adverse events, such as chills, fever, and headache, due to the cytokine release induced by vaccine. The time of disease progression was not modified with statistical significance, but an increase of overall survival (OS) (25.9 months versus 21.4, and 19.0 months versus 15.7, respectively) was reported in two studies that analysed Sipuleucel-T versus placebo in asymptomatic mCRPC patients.[37,38] Results from the IMPACT study,[37] which enrolled asymptomatic, symptomatic, or minimally symptomatic mCRPC patients, highlighted a 4.1 month improvement in the median OS and no significant difference in time to disease progression (14.6 weeks versus 14.4 weeks).[39] A decline in PSA was reported in <10% patients.

Several studies were focussed on further understanding the immune pathway induced by Sipuleucel-T, as well as on identifying biomarkers that better correlate with clinical outcomes for therapies like Sipuleucel-T.

An open-label Phase II neoadjuvant trial[40] showed that Sipuleucel-T induced infiltration of T cells into the tumour and recruitment of activated effector T cells (CD4+ and CD8+) into the PCa microenvironment, an increase of T cells with an activated phenotype at the tumour-stroma interface, and a systemic antigen specific T cell response.[41]

Additionally, Sipuleucel-T elicits IgG production against PAP and non-target tumour antigens, which are believed to contribute to the clinical efficacy of this vaccine.[42] Moreover, the improvement of OS induced by Sipuleucel-T may be correlated to the long-lasting antigen-specific cytotoxic T cells and to the resulting tumour cell death.[43] The promotion of a Th1 immune response was associated with a PSA decline too.[44]

Sipuleucel-T, like other immunotherapies, seems to be mostly effective in patients with a low tumour burden and a less compromised immune system.[13]

DCVAC/PCa

DCVAC/PCa represents another type of DC-based vaccine and consists of autologous poly I:C-activated DC loaded with a PSA-positive PCa human cell line, LNCaP, ultraviolet irradiated for safety.[45] Multiple Phase I/II clinical trials have explored the effects of the combination of this vaccine with docetaxel or with radiotherapy, as discussed later.[45,46]

Blood Dendritic Cell Antigens/1 BDC-01

Blood dendritic cell antigen (BDCA)/1 BDC-01 is an autologous vaccine prepared by pulsing autologous CD1+ cells from leukapheresis with a cocktail of HLA-A*0201-restricted peptides (PSA, PAP, PSMA, and control influenza peptide) mixed with keyhole limpet haemocyanin. The vaccine has been shown to be well tolerated, but no modification of disease was noted and PSA levels remained unchanged.[47]

PROSTVAC-VF

PROSTVAC-VF (PSA-TRICOM) uses two different recombinant pox-virus vectors encoding transgenes for TRICOM, containing a triad of T cell costimulatory molecules (LFA-3, B7.1, and ICAM-1), and PSA as primary immunotherapy, followed by boosters employing fowlpox. The vaccinia virus acts as an immunogenic vector; the infected cells undergo necrosis, releasing PSA that is subsequently processed by immature DC. Cell necrosis also releases pro-inflammatory signals that can further activate more DC.[48] These mechanisms induce T cell-specific immune response against PSA with an increase in median survival of 8–9 months and a reduced mortality rate.[49] A large international Phase III trial of asymptomatic or minimally symptomatic mCRPC treated with PROSTVAC-VF combined with GM-CSF was halted prematurely because no OS benefit was seen.[50]

A randomised Phase II placebo-controlled, double-blind trial of PSA-TRICOM was conducted to analyse its immunologic and

clinical effects in localised PCa;[17] it was well-tolerated and induced a significant increase in CD4+ and CD8+ cells.[51]

GVAX

GVAX (i.e., GM-CSF tumour cell vaccine) uses two PCa cell lines, LNCaP (androgen-sensitive derived from a lymph node metastasis) and PC3 (androgen-insensitive derived from bone metastasis), as the antigen source, genetically modified to express GM-CSF and then irradiated for safety.[52]

Two Phase III trials were performed, which showed good toleration and an increase of immunogenic response, parallel to an increase of OS rates; however, both trials were discontinued early because of the low probability to meet their primary endpoint, indicated in duration of survival.[13,52]

Listeria Monocytogenes Vaccine

Listeria monocytogenes (Lm) vaccine uses *Listeria,* an intracellular pathogenic bacterium that directly targets and activates DC, inducing both innate and adaptive immune responses against encoded heterologous antigens.[53] Two modified *Lm*, lacking their pathogenic features but maintaining their immunogenicity, have been developed for PCa. One, ADXS31-142, a vaccine with a live attenuated *Lm*-listeriolysin O (LLO) targeting PSA, was constructed to secrete an antigen-adjuvant fusion protein, consisting of a truncated fragment of the LLO fused to PSA. *Lm*-LLO/PSA caused regression of established PSA expressing tumours and induced specific cellular immune responses in mice, represented by a lower number of tumour infiltrating Tregs and T cells specific for PSA that recognise and lyse PSA-peptide pulsed target tumour cells.[54] ADXS31-142 is ongoing in mCRPC patients. Phase I/II, open-label, multicentre, non-randomised trials[22] are evaluating the safety and tolerability of ADXS31-142 alone and in combination with pembrolizumab, a programmed death receptor 1 (PD-1) inhibitor.[54]

The other *Listeria* vaccine, ADU-741, live attenuated double deleted, involves a strain with the deletion of two virulence genes, actA and internalin B, and it is engineered with several prostate-associated antigens.[55] Currently, a Phase I clinical trial has investigated the optimum dose of ADU-741 to induce immunogenicity in patients with mCRPC.[56] Vaccination therapies are summarised in Figure 1.

IMMUNE CHECKPOINT INHIBITORS

Tumour cells can also escape from the immune system through pathways involving immune checkpoints; these recognise surface-expressed ligands on self-tissues and dampen unwanted immune activation maintaining homeostasis and self-tolerance.[57] Several immune checkpoint inhibitors (ICI) that target such molecules expressed on immune or tumour cells are under evaluation as to whether they enhance the antitumour immune response.

CTLA-4, expressed on activated T cells and Tregs, downregulates the extent of T cell activation by determining the balance with CD28 signals. CTLA-4 binds the ligands B7-1 (CD80) and B7-2 (CD86) with a higher affinity than CD28.[58] The binding to CTLA-4 limits T cell expansion.[59]

IPILIMUMAB

Ipilimumab, a fully humanised monoclonal antibody that binds and blocks CTLA-4, restoring an anti-tumour immune response, was the first molecule FDA-approved in 2011 for advanced melanoma. Currently, many clinical trials with this drug are ongoing on several different types of tumours, including PCa tumours.

Two Phase III studies analysing the effects of combining ipilimumab with a low dose of radiotherapy in chemotherapy-naïve asymptomatic or minimally symptomatic mCRPC, showed that ipilimumab had no benefit in OS, but slightly improved PFS, suggesting a possible antitumour activity.[60] PD-1, a transmembrane glycoprotein predominantly expressed on T cells, interacts with PD-L1 and PD-L2 expressed on antigen-presenting cells, promoting tolerance and preventing tissue damage during chronic inflammation.

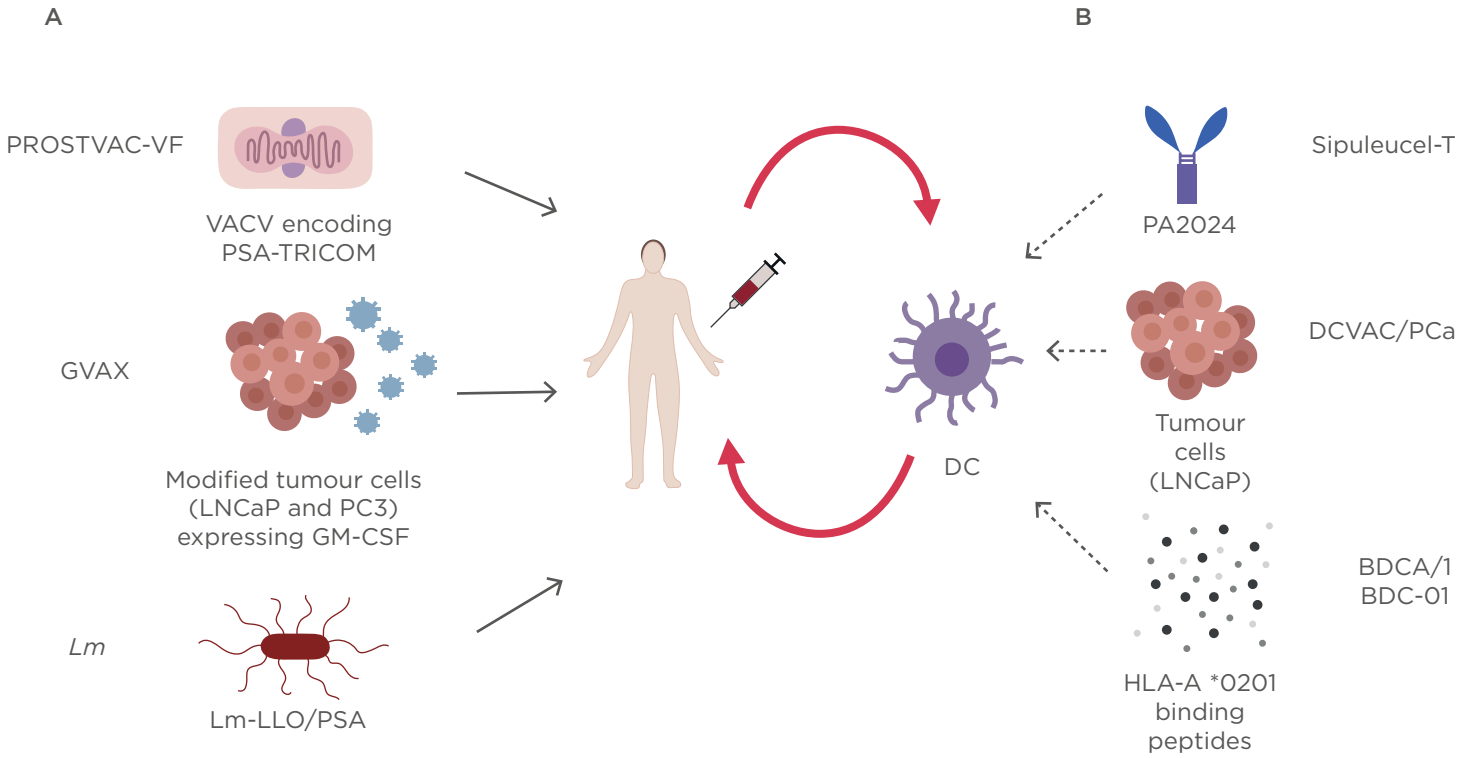

Figure 1: Current mentioned vaccination strategies for prostate cancer.

A) These compounds are directly injected into the patient: vaccinia (primary immunotherapy) and fowlpox (employed for 6 boosters), both engineered with recombinant poxvirus that express PSA and 3 costimulatory molecules named TRICOM (LFA-3, B7.1, and ICAM-1), are used in PROSTVAC-VF; two modified ultraviolet-killed tumour cell lines, androgen sensitive derived from a lymph node metastasis, and androgen insensitive derived from bone metastasis (PC3), express GM-CSF in GVAX; recombinant live attenuated *Lm* that expresses and secretes PSA fused to a non-functional LLO in Lm-LLO/PSA.

B) Dendritic cells are first harvested via leukapheresis from the patient, then activated *ex vivo*, expanded, and reinfused in the same patient. Dendritic cells are activated with: recombinant fusion protein (PA2024) consisting of PAP and GM-CSF in Sipuleucel-T; LNCaP cells incorporated with Poly I:C in DCVAC/PCa; or HLA-A*0201 binding peptides PSA, PAP, PSMA, and control influenza peptide mixed with keyhole limpet haemocyanin in BDCA/1 BDC-01. The activated dendritic cells are expanded and reinfused into the same patient.

GM-CSF: granulocyte-macrophage colony-stimulating factor; Lm: Listeria monocitogenes; Lm-LLO: Listeria monocitogenes -listeriolysin O; LNCaP: lymph node metastasis; PAP: prostatic acid phosphatase; PCa: prostate cancer; Poly I:C: polyinosinic-polycytidylic acid; PSA: prostate specific antigen; PSMA: prostate specific membrane antigen.

The interaction of PD-1/PD-L1 is the principal mediator of immune suppression and represents one of pivotal mechanism of immune escape by tumours.[61] PD-1/PD-L1 blockade could restore immune functions, resulting in a reduction of tumour mass and metastatic spread. Generally, PCa shows upregulation of PD-L1 expression as an adaptive response to changes in the immune microenvironment and PD-L1 is expressed by primary PCa and is increased in mCRPC.[62] This is the rationale of targeting PD-1/PD-L1 for the treatment of mCRPC.

Nivolumab

Nivolumab is a human IgG4 anti PD-1 and is FDA-approved for metastatic melanoma and for other tumours. No objective responses were reported in PCa treated with nivolumab. Indeed, only 1 of 17 patients with CRPC enrolled in a nivolumab trial showed a 28% reduction in measurable lesions.[58]

Pembrolizumab

Pembrolizumab is a humanised antibody targeting PD-1 and is FDA-approved for

metastatic melanoma and recently for any unresectable or metastatic solid tumour with certain genetic anomalies (mismatch repair deficiency or microsatellite instability). It has shown a favourable side effect profile in mCRPC.[63] The clinical benefits are under evaluation in monotherapy and in combination therapy.[25]

COMBINED THERAPY

Combination regimens have been proposed to optimise tumour immunogenicity and immune response in PCa. Several trials are evaluating the combination of different immune response modulators and the combination of immunotherapy with conventional therapies to improve cancer management.

For example, a combined therapy using different compounds targeting immune checkpoint blockade has been applied to PCa patients harbouring mutations in DNA-repair genes and shown encouraging clinical results.[13] Mateo et al.[48] have demonstrated that DNA repair defects (DRD) are detected in mCRPC patients during cancer progression: in 50 previously treated mCRPC patients, 16 patients associated with DNA repair defects in tumour cells showed a response to olaparib. Therefore, PARP inhibitors (PARPi), such as olaparib, could be a promising therapy.[64] PARPi induce cell death and lead to an increased mutational load in cancer cells. *In vitro* studies and mouse models have shown that PARPi enhance IFN and TIL, decrease myeloid-derived suppressor cells, and also induce PDL-1.[65] These data support the rationale for combining PARPi and ICI. A radiographic and/or PSA positive response was reported in patients treated with durvalumab, a human Ig blocking PD-L1, and olaparib.[28,66]

Moreover, combined ipilimumab and nivolumab was also evaluated in AR-V7-expressing mCRPC, an aggressive phenotype with poor PFS and OS, characterised by the expression of a mutated AR. Preliminary evidence suggested that AR-V7-positive tumours may be enriched for DRD, perhaps rendering them more sensitive to ICI. Ipilimumab plus nivolumab demonstrated encouraging efficacy in 40% of AR-V7-positive PCa with DRD mutations.[24,67]

Durvalumab with or without tremelimumab, a fully human monoclonal antibody anti-CTLA-4, is in Phase II study[29] with mCRPC patients, addressed to evaluate safety, tolerability, and interference with the growth and spread of the tumour.

ADT can synergise with ICI. Indeed, it is reported that ADT initially elicits a short-lived antitumour Th1-type response, but subsequently it can stimulate immunosuppressive lymphocyte subsets. MDV3100 induces an increase of natural killer cells and a decrease in myeloid-derived suppressor cells. On the other hand, MDV3100 upregulates PD-1/PD-L1 in resistant MDV3100 tumour cells and DC giving the premise for the pembrolizumab efficacy.[68] Pembrolizumab was added to MDV3100 in patients with progression and this Phase II trial reported a durable decline of PSA in a subset of patients and a radiographic positive response.[26,69]

The efficacy and safety of atezolizumab, another anti PD-L1, is under investigation in a Phase III randomised, multicentre trial, combined with MDV3100 and also compared with MDV 3100 alone in mCRPC patients who progressed after abiraterone acetate.[30]

Another combining therapy concerns vaccines with ICI. A murine model showed that the increase of immune response was counteracted by expression of PD-1 on antigen-specific CD8+ T cells elicited with immunisation. However, the blockade of PD-1/PD-L1 during T cell activation with immunisation led to superior antitumour efficacy.[70] Furthermore, patients previously immunised with either Sipuleucel-T or with a cancer vaccine containing plasmid DNA encoding human PAP (pTVG-HP) developed PD-1-regulated immune responses. Additionally, after vaccination, circulating tumour cells showed increased expression of PD-L1.[71]

Moreover, Th1 promotion induced by Sipuleucel-T correlated with a PSA decline while a PSA progression correlated with the upregulation of genes associated to CTLA-4, again suggesting the possible role of these checkpoints in dampening treatment-induced immune responses.[44] Based on this rationale, a clinical trial combining Sipuleucel-T with ipilimumab is ongoing for mCRPC.[14]

When combined therapies are chosen, identifying the best sequence is important. Recently, in a Phase II trial, identified as STAND,[72] patients with biochemically recurrent PCa were treated with Sipuleucel-T and ADT. When Sipuleucel-T was administered prior to ADT, a superior cellular immune response was induced, about 2-fold higher than the reverse sequence.

The cancer vaccine pTVG-HP combined with pembrolizumab was evaluated in mCRPC patients and its efficacy was augmented by concurrent PD-1 blockade. The development of PAP-specific Th1 and CD8+ T cell infiltration of the tumour was associated with a PSA decline, leading to a shrinkage of the tumour in some patients. More results are expected from the indicated study.[73]

The DCVAC/PCa vaccine in patients with mCRPC that have already received docetaxel induced an immune modulation, as indicated by the increase of antigen-specific T cell against PSA, detected after the fourth dose, and a significant decrease in the frequency of Tregs. Following 12 doses, the median PSA doubling time (PSADT) had increased from 5.67 prior to immunotherapy to 18.85 months.[46,47] Other studies including more patients and longer times of follow up are needed.[16]

PROSTVAC-VF combined with escalating doses of ipilimumab in 30 patients with mCRPC resulted in a decline in PSA in 58.0% of patients, and 73.3% of patients remained alive after 24 months versus 53% of patients treated with PROSTVAC-VF alone. Approximately 20% of patients treated with PROSTVAC-VF plus ipilimumab at higher doses remained alive at 80 months.[49] A Phase II study focussed on immune response[18] and a Phase I/II study of PROSTVAC-VF added to nivolumab with or without ipilimumab, with safety and changes in T cell infiltration as the primary endpoints, is ongoing.[19] Furthermore, PROSTVAC-VF plus docetaxel[20] or MDV3100[21] are under evaluation.

A trial combining *Lm*LLO/PSA with pembrolizumab is also ongoing, the first results of which show that this combination appears safe and tolerable, and showed promising activity compared to monotherapy. More analyses are underway in this trial.[22]

Recent data show that radium-223 induces T cell-mediated lysis in different tumour types, including PCa tumours;[74] therefore, combining this drug with immunotherapies may have additional clinical benefit. Radium-223 combined with pembrolizumab,[27] atezolizumab,[31] or Sipuleucel-T[15] is under evaluation in Phase I and Phase II studies.[4] Similarly, radiotherapy is currently undergoing Phase III study combined with ProstAtak (AdV-tk + valacyclovir), a viral cancer vaccine.[23]

ADOPTIVE T CELL THERAPY

Adoptive T cell therapy is another strategy for achieving an effective immune response against tumours. In this therapy, T cells from patients are genetically engineered and then reinfused. The development of chimeric antigen receptors (CAR) permits the targeting of tumour antigens with lower restrictions, such as TIL or lymphocytes genetically engineered to express a relevant T cell receptor. In CAR-T therapy, the specificity of antibodies is associated with cytotoxic activity of T cells to target tumour cells. Autologous T cells from patient are engineered *ex vivo* to express a CAR directed against TAA and are then reinfused back to the patient, to recognise and destroy tumour cells.

However, CAR-T can also induce many adverse effects that restrict the efficacy of such therapies.[75]

Until now, CAR-T targeting CD19 cells have been reported in studies to be a success in the treatment of haematological malignancies, and tisagenlecleucel was FDA-approved in 2017 for children and young adults with leukaemia. The application of this strategy to solid tumours is still being developed.

In a PCa mouse model, CAR-T cells constructed with anti-PSMA and CD28 as costimulatory molecules induced a near complete disappearance of the tumour in 3 weeks.[76] A recent Phase I trial,[32] using PSMA CAR-T cells, induced a reduction of PSA in two of five treated patients, and it was speculated that the lowering of plasma IL-2 interfered negatively.[77]

CONCLUSION

Until now, immunotherapy for PCa has shown less efficacy compared to in some other tumours.[58,78] Low mutational burden and a suppressive tumour microenvironment may negatively affect immunotherapy in PCa. Combinations of therapies, either involving multiple immunotherapies and/or standard chemotherapy, radiotherapy, and hormone therapy, might improve treatment outcomes and are under evaluation. It will also be necessary to determine the strategies to optimise timing and sequencing of combination therapy for maximal efficacy.

References

1. Siegel RL et al. Cancer statistics, 2018. Ca Cancer J Clin. 2018;68(1):7-30.
2. Cheng HH et al. Advanced clinical states in prostate cancer. Urol Clin North Am. 2012;39(4):561-71.
3. Bryce AH, Antonarakis ES. Androgen receptor splice variant 7 in castration-resistant prostate cancer: Clinical considerations. Int J Urology. 2016;23(8):646-53.
4. Wilson JM, Parker C. The safety and efficacy of radium-223 dichloride for the treatment of advanced prostate cancer. Expert Rev Anticancer Ther. 2016;16(9):911-8.
5. Mittal D et al. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014;27:16-25.
6. Gabrilovich DI et al. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012;12(4):253-68.
7. Drake CG. Prostate cancer as a model for tumour immunotherapy. Nat Rev Immunol. 2010;10(8): 580-93.
8. McArdle PA et al. The relationship between T-lymphocyte subset infiltration and survival in patients with prostate cancer. Br J Cancer. 2004;91(3):541-3.
9. Lanciotti M et al. The role of M1 and M2 macrophages in prostate cancer in relation to extracapsular tumor extension and biochemical recurrence after radical prostatectomy. Biomed Res Int. 2014;2014:486798.
10. Idorn M et al. Correlation between frequencies of blood monocytic myeloid-derived suppressor cells, regulatory T cells and negative prognostic markers in patients with castration-resistant metastatic prostate cancer. Cancer Immunol Immunother. 2014;63(11):1177-87.
11. Liu Y et al. Dendritic and lymphocytic cell infiltration in prostate carcinoma. Histol Histopathol. 2013;28(12):1621-8.
12. Krueger TE et al. Tumor- infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? Prostate. 2018;79(3):320-30.
13. Cordes LM et al. Perspectives on the clinical development of immunotherapy in prostate cancer. Asian J Androl. 2018;20(3):253-9.
14. University of California, San Francisco. A randomized Phase 2 trial of combining Sipuleucel-T with immediate vs. delayed CTLA-4 blockade for prostate cancer. NCT01804465. https://clinicaltrials.gov/ct2/show/NCT01804465.
15. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Study of Sipuleucel-T w/ or w/o radium-223 in men with asymptomatic or minimally symptomatic bone-MCRPC. NCT02463799. https://clinicaltrials.gov/ct2/show/NCT02463799.
16. Sotio a.s. Phase III Study of DCVAC added to standard chemotherapy for men with metastatic castration resistant prostate cancer (VIABLE). NCT02111577. https://clinicaltrials.gov/ct2/show/NCT02111577.
17. National Cancer Institute (NCI). PROSTVAC (PSA-TRICOM) in preventing disease progression in patients with localized prostate cancer undergoing active surveillance. NCT02326805. https://clinicaltrials.gov/ct2/show/NCT02326805
18. University of California, San Francisco. Neoadjuvant PROSTVAC-VF with or without Ipilimumab for prostate cancer. NCT02506114. https://clinicaltrials.gov/ct2/show/NCT02506114.
19. National Cancer Institute (NCI). PROSTVAC in combination with Nivolumab in men with prostate cancer. NCT02933255. https://clinicaltrials.gov/ct2/show/NCT02933255.
20. National Cancer Institute (NCI). Docetaxel and PROSTVAC for metastatic castration-sensitive prostate cancer. NCT02649855. https://clinicaltrials.gov/ct2/show/NCT02649855.
21. Advaxis, Inc. Enzalutamide in combination with PSA-TRICOM in patients with non-metastatic castration sensitive prostate cancer. NCT01875250.https://clinicaltrials.gov/ct2/show/NCT01875250.
22. Advaxis, Inc. ADXS31-142 alone and in combination with pembrolizumab (MK-3475) in patients with prostate cancer - KEYNOTE-046. NCT02325557. https://clinicaltrials.gov/ct2/show/NCT02325557.
23. Advantagene, Inc. Phase 3 Study of ProstAtak® immunotherapy with standard radiation therapy for localized prostate cancer (PrTK03). NCT01436968. https://clinicaltrials.gov/ct2/show/NCT01436968.
24. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Biomarker-driven therapy with Nivolumab and Ipilimumab in treating patients with metastatic hormone-resistant prostate cancer expressing AR-V7 (STARVE-PC). NCT02601014. https://clinicaltrials.gov/ct2/show/NCT02601014.
25. Merck Sharp & Dohme Corp. Study of Pembrolizumab (MK-3475) combination therapies in metastatic castration-resistant prostate cancer (MK-3475-365/KEYNOTE-365). NCT02861573. https://clinicaltrials.gov/ct2/show/NCT02861573.
26. OHSU Knight Cancer Institute. Pembrolizumab in treating patients with metastatic castration resistant prostate cancer previously treated with Enzalutamide. NCT02312557. https://clinicaltrials.gov/ct2/show/NCT02312557.
27. Dana-Farber Cancer Institute. Study evaluating the addition of Pembrolizumab to radium-223 in mCRPC. NCT03093428. https://clinicaltrials.gov/ct2/show/NCT03093428.
28. National Cancer Institute (NCI). Phase I/II study of the anti-programmed Death Ligand-1 antibody MEDI4736 in combination with Olaparib and/or Cediranib for advanced solid tumors and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers. NCT02484404. https://clinicaltrials.gov/ct2/show/NCT02484404.
29. M.D. Anderson Cancer Center. Tremelimumab + Durvalumab chemotherapy naive CRPC. NCT03204812. https://clinicaltrials.

gov/ct2/show/NCT03204812.

30. Hoffmann-La Roche. A study of Atezolizumab (anti-PD-L1 antibody) in combination with Enzalutamide in participants with metastatic castration-resistant prostate cancer (mCRPC) after failure of an androgen synthesis inhibitor and failure of, ineligibility for, or refusal of a Taxane regimen (IMbassador250). NCT03016312. https://clinicaltrials.gov/ct2/show/NCT03016312.
31. Hoffmann-La Roche. Safety and tolerability of Atezolizumab (ATZ) in combination with radium-223 Dichloride (R-223-D) in metastatic castrate-resistant prostate cancer (CRPC) progressed following treatment with an androgen pathway inhibitor. NCT02814669. https://clinicaltrials.gov/ct2/show/NCT02814669.
32. Memorial Sloan Kettering Cancer Center. Adoptive transfer of autologous T cells targeted to Prostate Specific Membrane Antigen (PSMA) for the treatment of Castrate Metastatic Prostate Cancer (CMPC). NCT01140373. https://clinicaltrials.gov/ct2/show/NCT01140373.
33. Joniau S et al. Current vaccination strategies for prostate cancer. Eur Urol. 2012;61(2):290-306.
34. Sims RB. Development of sipuleucel-T: Autologous cellular immunotherapy for the treatment of metastatic castrate resistant prostate cancer. Vaccine. 2012;30(29):4394-7.
35. Matera L. The choice of the antigen in the dendritic cell-based vaccine therapy for prostate cancer. Cancer Treat Rev. 2010;36(2):131-41.
36. Small EJ et al. Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells. J Clin Oncol. 2000;18(23):3894-903.
37. Small EJ et al. Placebo-controlled phase III trial of immunologic therapy with Sipuleucel-T(APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006;24(19):3089-94.
38. Higano CS et al. Integrated data from 2 randomized, double-blind, placebo-controlled, Phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009;115(16):3670-9.
39. Kantoff PW et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl. J Med. 2010;363(5):411-22.
40. Dendreon. Sipuleucel-T as neoadjuvant treatment in prostate cancer (NeoACT). NCT00715104. https://clinicaltrials.gov/ct2/show/NCT00715104.
41. Fong L et al. Activated lymphocyte recruitment into the tumor microenvironment following preoperative Sipuleucel-T for localized prostate cancer. J Natl Cancer Inst. 2014;106(11):1-9.
42. GuhaThakurta D et al. Humoral immune response against nontargeted tumor antigens after treatment with Sipuleucel-T and its association with improved clinical outcome. Clin Cancer Res. 2015;21(16):3619-30.
43. Antonarakis ES et al. Antigen-specific CD8 lytic phenotype induced by Sipuleucel-T in hormone-sensitive or castration-resistant prostate cancer and association with overall survival. Clin Cancer Res. 2018;24(19):4662-71.
44. Hagihara K et al. Neoadjuvant Sipuleucel-T induces both Th1 activation and immune regulation in localized prostate cancer. Oncoimmunology. 2018;8(1):1-6.
45. Podrazil M et al. Phase I/II clinical trial of dendritic-cell based immunotherapy (DCVAC/PCa) combined with chemotherapy in patients with metastatic, castration-resistant prostate cancer. Oncotarget. 2015;6(20):18192-205.
46. Fucikova J et al. Phase I/II trial of dendritic cell-based active cellular immunotherapy with DCVAC/PCa in patients with rising PSA after primary prostatectomy or salvage radiotherapy for the treatment of prostate cancer. Cancer Immunol Immunother. 2018;67(1):89-100.
47. Prue RL et al. A Phase I clinical trial of CD1c (BDCA-1) + dendritic cells pulsed with HLA-A*0201 peptides for immunotherapy of metastatic hormone refractory prostate cancer. J Immunother. 2015;38(2):71-6.
48. Madan RA et al. Prostvac-VF: A vector-based vaccine targeting PSA in prostate cancer. Expert Opin Investig Drugs. 2009;18(7):1001-11.
49. Kantoff PW et al. Revised overall survival analysis of a Phase II, randomized, double-blind, controlled study of PROSTVAC in men with metastatic castration-resistant prostate cancer. J Clin Oncol. 2017;35(1):124-5.
50. Bavarian Nordic. A randomized, double-blind, Phase 3 efficacy trial of PROSTVAC-V/F +/- GM-CSF in men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (Prospect). NCT01322490. https://clinicaltrials.gov/ct2/show/NCT01322490.
51. Parsons JK et al. A randomized, double-blind, Phase II trial of PSA-TRICOM (PROSTVAC) in patients with localized prostate cancer: The immunotherapy to prevent progression on active surveillance study. Eur Urol Focus. 2018;4(5):636-8.
52. Higano CS et al. Phase 1/2 dose escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. Cancer. 2008;113(5):975-84.
53. Shahabi V et al. Development of a Listeria monocytogenes based vaccine against prostate cancer. Cancer Immunol Immunother. 2008;57(9):1301-13.
54. Haas NB et al. Phase I-II study of ADXS31-142 alone and in combination with pembrolizumab in patients with previously treated metastatic castration-resistant prostate cancer (mCRPC): The KEYNOTE-046 trial. J Immunother Cancer. 2015;3(Suppl 2):P153.
55. Flickinger JC Jr et al. Listeria monocytogenes as a vector for cancer immunotherapy: Current understanding and progress. Vaccines (Basel). 2018;6(3):48.
56. Janssen Research & Development, LLC. Safety & immunogenicity of JNJ-64041809, a live attenuated double-deleted listeria immunotherapy, in participants with metastatic castration-resistant prostate cancer. NCT02625857. https://clinicaltrials.gov/ct2/show/NCT02625857.
57. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-5.
58. Bracarda S et al. Immunologic checkpoints blockade in renal cell, prostate, and urothelial malignancies. Semin Oncol. 2015;42(3):495-505.
59. Hodi FS et al. Improved survival with Ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
60. Small EJ et al. Pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. Clin Cancer Res. 2007;13(6):1810-5.
61. McDermott DF, Atkin MB. PD-1 as a potential target in cancer therapy. Cancer Med. 2013;2(5):662-73.
62. Haffner MC et al. Comprehensive evaluation of programmed Death-Ligand 1 expression in primary and metastatic prostate cancer. Am J Pathol. 2018;188(6):1478-85.
63. Hansen AR et al. Pembrolizumab for advanced prostate adenocarcinoma: Findings of the KEYNOTE-028 study. Ann Oncol. 2018;29(8):1807-13.
64. Mateo J et al. DNA-repair defects and Olaparib in metastatic prostate cancer. N Engl J Med. 2015;373:1697-708.
65. Dréan A et al. PARP inhibitor combination therapy. Crit Rev Oncol Hematol. 2016;108:73-85.
66. Karzai F et al. Activity of Durvalumab plus Olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer. 2018;6(1):141.

67. Boudadi K et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. Oncotarget. 2018;9(47):28561-71.

68. Graff JN et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget. 2016;7(33):52810-7.

69. Graff JN et al. Pembrolizumab (Pembro) plus enzalutamide (Enz) in metastatic castration resistant prostate cancer (mCRPC): Extended follow up. J Clin Oncology. 2018;36:5047.

70. Zahm CD et al. Vaccination with high-affinity epitopes impairs antitumor efficacy by increasing PD-1 expression on CD8+ T Cells. Cancer Immunol Res. 2017;5(8):630-41.

71. Rekoske BT et al. Antitumor vaccination of prostate cancer patients elicits PD-1/PD-L1 regulated antigen-specific immune responses. Oncoimmunology. 2016;5(6):1165377.

72. Antonarakis ES et al. Sequencing of Sipuleucel-T and androgen deprivation therapy in men with hormone-sensitive biochemically recurrent prostate cancer: A Phase II randomized trial. Clin Cancer Res. 2017;23(10):451-9.

73. University of Wisconsin, Madison. Vaccine therapy and Pembrolizumab in treating patients with hormone-resistant, metastatic prostate cancer. NCT02499835. https://clinicaltrials.gov/ct2/show/NCT02499835.

74. Malamas AS et al. Sublethal exposure to alpha radiation (223Ra dichloride) enhances various carcinomas' sensitivity to lysis by antigen-specific cytotoxic T lymphocytes through calreticulin-mediated immunogenic modulation. Oncotarget. 2016;7(52):86937-47.

75. Boyiadzis MM et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: Clinical perspective and significance. J Immunother Cancer. 2018;6(1):137.

76. Zhang Q et al. Efficacy against human prostate cancer by prostate specific membrane antigen specific, Transforming Growth Factor b insensitive genetically targeted CD8+ T cells derived from patients with metastatic castrate resistant disease. Eur Urol. 2018;73(5):648-52.

77. Junghans RP et al. Phase I trial of anti-PSMA designer CAR-T Cells in prostate cancer: Possible role for interacting Interleukin 2-T cell pharmacodynamics as a determinant of clinical response. Prostate. 2016;76(14):1257-70.

78. Franklin C et al. Immunotherapy in melanoma: Recent advances and future directions. Eur J Surg Oncol. 2017;43(3):604-11.

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Physiotherapy in Post Neobladder Voiding Dysfunction in the Treatment of Malignant Neoplasm

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Abstract

Bladder cancer is a worldwide health problem, due to both its high prevalence and the cost related to the treatment. It is usually identified on the basis of visible blood in the urine or blood found on urine testing, but emergency admission is a common way for bladder cancer to present and is often associated with a poor prognosis. The contracted bladder is a rare and serious complication which is disabling. In these cases, there is a need for a neobladder, which may lead to voiding dysfunction. Physiotherapeutic avenues have demonstrated effectiveness in the treatment of voiding dysfunction; they rehabilitate the individual and improve their quality of life. This study reports the case of a male patient who underwent transurethral resection of a bladder tumour (high-grade T1 carcinoma), which developed complications during treatment with Bacillus Calmette-Guérin. He also underwent cystoprostatectomy with ileal orthotopic neobladder.

CONTEXT

Bladder cancer is a public health problem. In 2012, it was the ninth most common malignant neoplasia in the world. It has a high prevalence in several populations and its treatment has a high cost.[1,2] The American Cancer Society (ACS) estimated there would be 81,190 new cases of bladder cancer, 62,380 cases related to men and 18,810 to women, in the USA during 2018.[3]

With regard to Europe, in 2012 it was estimated there were 118,000 new cases and 52,000 deaths. Expenditures have been estimated at around €4.9 billion in the European Union (EU).[4] The majority (90%) of cases of bladder cancer are urothelial carcinoma in Western Europe and in the USA. Squamous cell bladder cancer is more common in Africa, where schistosomiasis infections are more prevalent. Recent studies have shown that the USA and Western Europe reported particularly high incidence rates, while countries in Eastern Europe and Asia have the lowest rates.[4]

According to the Instituto Nacional de Câncer (National Cancer Institute, INCA), approximately 9,480 cases of bladder cancer were expected in Brazil during 2018: 6,690 cases in men and 2,790 in women.[4] There are risk factors associated with the development of bladder cancer, such as age and race, with elderly white men being the group most likely to develop this type of cancer. Smoking can increase the risk of developing bladder cancer. Another risk factor is exposure to various chemical compounds.[5] Of these cases, 75–85% are composed of non-muscle invasive tumours, meaning that the disease remains confined to the mucosa (Ta-CIS) or to the submucosa (T1); patients with this condition are potential candidates for complementary therapy with intravesical chemotherapy or immunotherapy.[1,6,7]

Since the introduction of intravesical immunotherapy using Bacillus Calmette–Guérin (BCG) as an adjuvant to treatment, a decrease in the rate of recurrence has been reported.[8] Although the use of BCG is considered to be effective, not all cases benefit from this treatment. Toxicity, varied complications, and lack of therapeutic response should be taken into account when proposing adjuvancy.[9,10]

The most common complications are easily resolved, but the contracted bladder is a rare and serious local complication which incapacitates the patient. It is mainly observed in individuals taking part in maintenance programmes.[10]

In refractory cases or with disabling symptoms, the indication is for cystoprostatectomy with reconstruction of intestinal neobladder. In some cases, after the neobladder reconstruction there is a need for auto-catheterisation, due to the difficulty of emptying and to the presence of urinary incontinence, nocturia, and enuresis.[9,10]

The incidence of incontinence after this surgery is reported as 30–60% and it is considered an adverse outcome. The incidence of urinary incontinence after orthotopic neobladder is related to the postoperative evaluation time, age of patients, method of surgery, and whether there is intraoperative preservation of nerves.[11] Therapeutic options have been limited to date and they include pharmacological treatment, surgical intervention, and pelvic floor physiotherapy.[12,13] Physiotherapeutic options are effective in the treatment of voiding dysfunction, which leads to rehabilitation and improved quality of life for the patient.[14]

CASE REPORT

This case report is a continuation of a previous case reported by Filho et al.[2] after follow-up by the pelvic urology and physiotherapy team. A 53-year-old male patient, who was a smoker, with no previous background, presented with painless macroscopic haematuria, which began 3 days before admission to the emergency department in 2009. He underwent ultrasonography of the urinary tract, which revealed an intravesical tumour on the left lateral wall.

Transurethral resection of the bladder tumour with a diagnosis of high-grade T1 urothelial carcinoma was performed. After 8 weeks, the patient underwent a new transurethral resection, this time without relapse or new lesions. Biopsies of the previously resected bed revealed cystitis. He started intravesical adjuvant therapy with BCG (Mycobacterium Bovis BCG, Ataulpho de Paiva Foundation, Rio de Janeiro, Brazil) after 1 month of the last surgical approach, with a total duration of 3 years. The total duration of the treatment followed the protocol of the service, with the induction phase performed for 8 weeks and the maintenance phase for 3 years (1 weekly cycle for 3 weeks, at 3 and 6 months, and every 6 months thereafter), both with a dose of 80 mg at each session.

In the second year of treatment, the patient did not relapse but had some symptoms of the lower urinary tract related to storage, such as frequent urination and voiding urgency without leakage. Despite this, he did not experience a significant deterioration in quality of life.

At the beginning of the third and last year of treatment, the urinary symptoms worsened, with an increase in urinary frequency (around 20 times a day), urgency with incapacitating urinary leakage, and suprapubic pain at any bladder filling. During this time, it was necessary to stop the treatment. Urethrocystography revealed a small capacity bladder, bilateral vesicoureteral reflux (degree I), and considerable post-voiding residue (Figure 1).

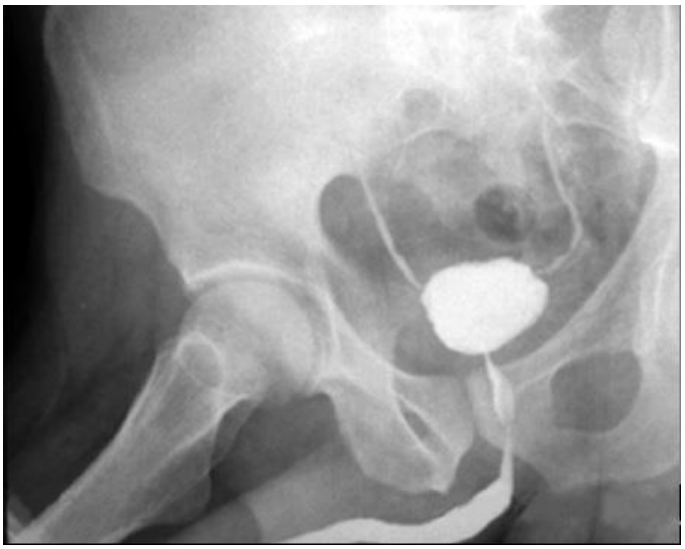

Figure 1: Image of urethrocystography in the third year of follow-up (maintenance phase with Bacillus Calmette-Guérin) after transurethral resection.

The urodynamic study demonstrated a very low bladder capacity (40 mL) with a very high sensitivity in this volume and high detrusor pressure (Pdet: 78cmH2O), which confirmed the case of contracted bladder. The cystoscopy of this period showed no neoplastic lesion; however, due to the incapacitating symptoms, the patient underwent cystoprostatectomy, ileal orthotopic neobladder, and lymphadenectomy.

In the intraoperative period, small bladder was evident with no other characteristics. The surgical procedure was uneventful. The patient evolved with ileal loop urinary fistula on the tenth postoperative day, with resolution based on conservative measures. With no other complications, he was discharged from hospital. He was followed up as an outpatient in a neobladder distension programme (Figure 2).

After 45 days, the patient presented with repetitive urinary leakage, nocturia, enuresis, absence of voiding desire, and increased urinary frequency, with daily use of four diapers. He was then referred to the pelvic physiotherapy team. Pelvic physiotherapy is considered the first indication of conservative treatment, level A, for pelvic floor dysfunctions involving micturition dysfunction.[15,16]

The patient had their pelvic-floor muscle function evaluated, which revealed a pelvic-floor muscle function of 1 (scale 0–5), pelvic floor muscles hypotonia, diurnal voiding (performed for 3 consecutive days) with a daytime frequency of 26 times per day, 18 losses per day, and 45g loss on the 1-hour pad test. A total of 12 physiotherapy sessions were performed twice a week with a duration of 1 hour per session. The resources used were anal intracavitary electrostimulation, with a frequency of 3,550 Hz, pulse width of 400–700 µs, and an intensity based on the observation of palpable or visible contractions that were comfortable for the patient; perineal exercises (performed in an outpatient setting and orientated to the home environment); behavioural re-education; and programmed micturition.

The perineal exercises were performed in 3 sets of 10 contractions sustained for 3 seconds, with a rest of 6 seconds, and 10 fast contractions 3 times a day. The behavioural re-education depended on the change of habits, i.e., water intake and toilet habits. The programmed micturition was adjusted every 2 hours initially and then every 3 hours during the day; during the night, 2 micturitions were programmed.

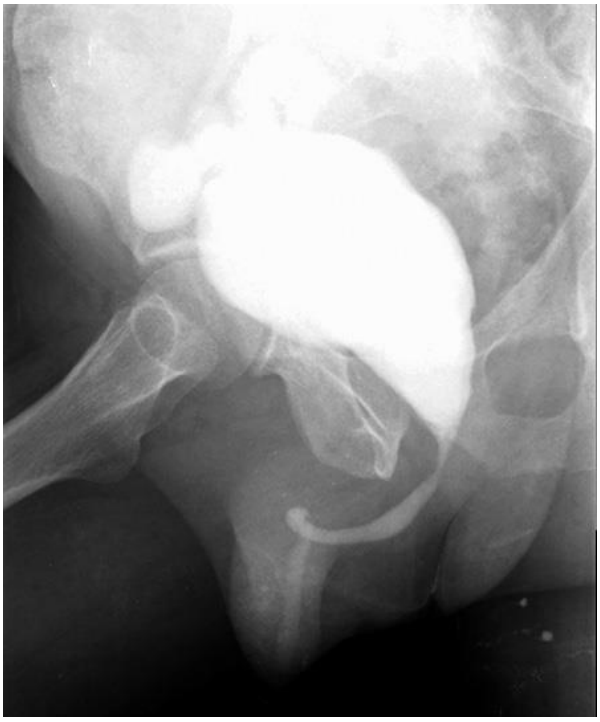

Figure 2: Image of urethrocistography while the patient was in an outpatient clinic undergoing a neobladder distension programme (late postoperative).

Table 1: Score of the variables observed in the evaluation, reassessment, evaluation at 3 months, and evaluation at 4 years after the physiotherapeutic treatment.

	Evaluation January 2013	Re-evaluation May 2013	Re-evaluation August 2013	Re-evaluation August 2017
Pelvic floor muscle function*	1	3	3	2
Daytime voiding frequency	26	6	6	6
Nocturia	6	1	1	2
Enuresis	2	0	0	0
Stress incontinence	18	3 (drop)	3 (drop)	3 (drop)
Diapers	6	2 mini absorbents	2 mini absorbents	2 mini absorbents
Pad test	45 g	0 g	0 g	2 g

*The modified Oxford scale was used to evaluate pelvic floor muscle function.

At the end of the sessions, the patient was reassessed. He was first followed-up for 3 months after the sessions and then after 4 years (Table 1).

FINAL CONSIDERATIONS

The contracted bladder, which is an uncommon complication but one of the most serious, occurs in <1% of individuals.[1,8] This complication should be suspected in patients with intense urinary symptoms at any stage and especially in the maintenance of BCG immunotherapy.[7,10] In the present study, the first case of bladder contraction in a patient during the combined therapy of the authors' service was described.[9] He evolved to cystoprostatectomy with reconstruction of intestinal neobladder, which resulted in voiding dysfunction.

Reports of voiding dysfunction as a consequence of neobladder have been present in the scientific literature for some years. Hautmann et al.[17] followed 211 men for 3 years undergoing reconstruction of the lower urinary tract by means of the ileal neobladder. In this study, 5.5% of the patients did not present with nocturia and enuresis, 6.0% used daily protection, and the remaining patients presented with mild-to-moderate urinary incontinence.

Urinary incontinence impacts the lives of individuals physically, psychologically, and socially. Patients have physical limitations, changes in social and occupational activities, influences on their emotional state and sexual life, as well as social and hygienic discomfort, fear of urinary loss, the smell of urine, the need to use protectors, and the need to change clothes more frequently.[18] Nocturia can often disrupt sleep and lead to fatigue, depression, and social isolation.[19] In the present case, the patient initially had a voiding frequency of 26 times per day and nocturia 6 times per night, leading to the withdrawal of his professional and social life. He presented with altered sleep and mood.

Mateo et al.[20] verified postoperative voiding continence between open and laparoscopic surgery in radical cystectomy with ileal orthotopic neobladder. Of the 72 patients operated on, 4 required auto-catheterisation, 1 underwent open surgery, and 3 underwent laparoscopy. Regarding urinary incontinence, 6 patients from the open surgery, and 11 from the laparoscopy evolved with urinary incontinence. In the present case, the patient presented with stress incontinence, enuresis, and nocturia, without the need for auto-catheterisation. With pelvic physiotherapy, there was a significant improvement of the urinary symptoms over the short, medium, and long-term, as shown in Table 1.

Pelvic physiotherapy is the first-line conservative treatment for voiding dysfunctions, as in the

case of urinary incontinence.[21] It is a non-invasive, low-cost resource with few contraindications. In the literature, studies about voiding dysfunctions and the use of physiotherapy after surgical correction with cystoprostatectomy and ileal neobladder are scarce. Therefore, further studies are needed to verify the importance of pelvic physiotherapy in such dysfunctions. The success of the physiotherapeutic approach in the present case report is highlighted.

CONCLUSION

The physiotherapeutic intervention in voiding dysfunction after ileal neobladder was effective as a treatment in the reported case, improving the quality of life of the patient. However, the authors suggest that new studies should be carried out with larger series of cases from different centres to compare with these results.

References

1. Koya MP et al. Complications of intravesical therapy for urothelial cancer of the bladder. J Urol. 2006;175(6):2004-10.
2. Filho JEV et al. Cystectomy with orthotopic ileal neobladder reconstruction for treatment of bladder contracture after intravesical bacillus Calmette-Guerin therapy. Einstein (São Paulo). 2014;12(4).
3. American Cancer Society. Bladder Cancer. Available at: https://cancer.org/cancer/bladder-cancer.html. Last accessed: 12 July 2018.
4. Wong MCS et al. The global epidemiology of bladder cancer: A joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep. 2018;8(1):1129.
5. Instituto Nacional do Câncer (INCA). Câncer de bexiga. Available at: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/bexiga. Last accessed: 12 July 2018.
6. Hameed A et al. Bladder contracture: Review for intravesical bacillus Calmette-Guerin complication. Can J Urol. 2007;14(6):3745-9.
7. Çağri Şenocak et al. Hydrodistention and anticholinergics are useful for bladder contracture caused by intravesical BCG therapy: A case report. N J Med. 2011;28(3):185-7.
8. Lamm DL et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992;147(3):596-600.
9. Nieder AM et al. Cystoprostatectomy and orthotopic ileal neobladder reconstruction for management of bacilli Calmette Guérin-induced bladder contractures. Urology. 2005;65(5):909-12.
10. Manasia P et al. Small bladder and multiple urethral recurrences after intravesical instillation of bacillus Calmette-Guerin for superficial transitional cell carcinoma of the bladder. J Urol. 2001;165(2):529-30.
11. Zhang YG et al. Diagnosis and treatment of urinary incontinence after orthotopic ileal neobladder in China. Chin Med J (Engl). 2017;130(2):231-5.
12. Mayer M et al. [Stress urinary incontinence after radical cystectomy: Neobladder construction and placement of the functional retrourethral sling]. [In German].
13. Littlejohn N et al. Treatment of pelvic floor disorders following neobladder. Curr Urol Rep. 2017;18(1):5.
14. Zaidan P, Silva EB. [Pelvic floor muscle exercises with or without electric stimulation and post-prostectomy urinary incontinence: A systematic review]. Fisioter Mov. 2016.29(3):635-49. (In Portuguese).
15. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment for urinary incontinence in women. A Cochrane systematic review. Eur J Phys Rehabil Med. 2008;44(1):47-63.
16. Bo K et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. Int Urogynecol J. Neurourol Urodyn. 2017;36(2):221-44.
17. Hautmann RE et al. The ileal neobladder: 6 years of experience with more than 200 patients. J Urol. 1993;150(1):40-5.
18. Figueiredo EM et al. [Sociodemographic and clinical profile of users of Urogynecological Physiotherapy service of the public network]. Braz J Phys Ther. 2008;12(2):136-42. [In Portuguese].
19. Espuña PM, Puig Clota M. Coital urinary incontinence: Impact on quality of life as measured by the King's Health Questionnaire. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(5):621-5.
20. Mateo E et al. [Comparative study between open and laparoscopic approach in radical cystectomy with continent ileal orthotopic reservoir]. Actas Urol Esp. 2015;39(2):92-7. [In Spanish].
21. Moroni RM et al. Conservative treatment of stress urinary incontinence: A systematic review with meta-analysis of randomized controlled trials. Rev Bras Ginecol Obstet. 2016;38(2):97-111.

A Systematic Review of Scrotal Squamous Cell Carcinoma

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Abstract

The epidemiology of scrotal cancer has changed over time away from occupational exposure to soot. The current incidence of scrotal malignancy is approximately 1 per 1 million males per year. This review summarises the current literature on the management of scrotal squamous cell carcinoma (SCC), including pathogenesis, available diagnostic tools, current treatment, and overall management strategies.

The rarity of SSC cases makes it difficult to recruit patients for studies of this disease. To date, very few studies have been performed, and those that have been completed were limited by a small sample size. This review analyses all available evidence, which varies from retrospective case series to prospective multicentre trials.

Psoralen ultraviolet light A treatment and human papillomavirus infection are significant risk factors for this cancer. Scrotal SCC had lower survival rates compared with other histological subtypes and the 5-year relative survival rate was 77%. Many studies also showed a positive margin, even after wide excision of the lesion. Excision of the primary lesion and a risk-stratified approach for staging and treatment of regional lymph nodes is the mainstay of current management strategies. For patients with clinically negative lymph nodes, sentinel lymph node biopsy and PET scans for patients with suspected pelvic node involvement has improved the diagnostic yield. The new neoadjuvant therapy (both chemotherapy and radiotherapy) has helped to downstage the disease for complete resection.

The prognosis of scrotal SCC is determined by margin-free excision, depth of infiltration, and its histologic grade. Future trials focussing on the conjunction of SCC with penile cancer, as well as the creation of a multinational network for 'virtual' online multidisciplinary meetings, will help to improve the overall survival for scrotal SCC patients.

INTRODUCTION

Chimney sweeps' carcinoma was first described by Percivall Pott in 1775 who noted that the cancer was associated with occupational exposure to soot.[1] The cancer primarily affected chimney sweeps who had been in contact with soot since early childhood. The median age at the onset of symptoms was 37.7 years, although boys as young as 8 years old were found to have the disease.[2]

It was proposed by W.G. Spencer in 1890 that sweat running down their bodies had caused soot to accumulate in the rugae of the inferior surfaces of the scrotum, with the resulting chronic irritation causing scrotal cancer.[3] Back in 1840, a lengthy law was passed making it illegal for anyone under the age of 21 years to sweep chimneys and, in 1875, another law was passed that allowed only registered people to undertake the work, putting an end to the use of young chimney sweeps. These laws have decreased the incidence and changed the aetiology of scrotal cancer over time.[3] The current incidence of scrotal malignancy is approximately 1 per 1 milllion males/year, the same as for penile squamous cell carcinoma (SCC). The rarity of cases of this disease and our understanding of the changing nature of scrotal cancer is the focus of this review, which will summarise the current literature in terms of current scrotal SCC pathogenesis, diagnostic evaluation tools, current treatments, and overall updated management.

Scrotal cancer has a number of histologic sub types: SCC (35%), extramammary Paget's disease (22%), sarcoma (20%), basal cell carcinoma (17%), and melanoma and adnexal skin tumours (6%). SCC is the most common variety. The median (95% confidence interval [CI]) overall survival for localised low-risk scrotal cancers (basal cell carcinoma, extramammary Paget's disease, sarcoma) and localised high-risk scrotal cancers (melanoma, SCC, adnexal skin tumours) was 166 (145–188) and 118 (101–135) months, respectively.[4] Patients with regional and distant disease were reported to have poorer overall survival.[5]

The management and follow-up plans for scrotal SCC patients are not well documented in the literature. Surgical excision is the recommended treatment for localised disease, with confirmation of margin clearance. Wound closure can be performed with primary closure, skin grafts, flaps, or by secondary intention. Clear understanding of the management and survival outcomes of this disease can help the urologist to determine the appropriate course of treatment and patient care.

PATHOPHYSIOLOGY

Scrotal SCC was the first malignancy recorded to be linked directly to occupational exposure. Scrotal SCC has also been linked to exposure to tar, pitch, different types of lubricating and cutting oils, creosotes, gas production, and paraffin wax pressing.[6-11] As there has been a huge improvement in both working environments and the relevant laws in place, occupational risk factors have not been associated with increased risk of scrotal SCC over the last two decades.[12] A nationwide case control study found a significantly increased risk (odds ratio [OR]: 6.7; 95% CI: 1.0–45.6) of developing scrotal SCC with a cumulative lifetime duration of nude sunbathing of 26–150 hours. In addition, the results suggested that the use of sunbeds increases the risk of scrotal SCC (OR: 3.2; 95% CI: 1.0–10.4).[13]

Moreover, iatrogenic ultraviolet radiation for the treatment of skin diseases was also associated with a high risk of scrotal SCC. In a cohort of men with psoriasis, who had been treated with oral psoralen and ultraviolet A photochemotherapy (PUVA) and followed-up for 12.3 years, Stern et al.[14] found a risk ratio of 95.7 (95% CI: 43.8–181.8) for genital SCC in PUVA treated patients compared with the general population incidence rates. In patients exposed to high doses of PUVA, the incidence of invasive SCC was 16-times higher (95% CI: 9.4–26.4) than that of patients exposed to low doses. With a further 10 years of follow-up, Stern et al.[6] found a 52.6-fold (95% CI: 19.3–114.6) increase in the incidence of genital SCC in this cohort compared with that expected for the general Caucasian population. Conversely, the link between PUVA and SCC was not confirmed in European prospective studies with relatively short follow-up periods;[15] however, analysis of a large database, with an observation period of at least 14 years, showed a relative risk of 5.6–6.5 for SCC in European men.[16,17] The male genitalia seem to be more susceptible to the carcinogenic effects of PUVA than non-genital areas. The carcinogenic effects of the PUVA therapy include DNA damage accumulation and immunosuppression.[18] There was no increased risk of skin cancer reported in studies assessing the carcinogenic risk of narrow band ultraviolet B, which is used more commonly for treating psoriasis.[19]

Human papillomavirus (HPV) was previously linked to scrotal SCC. In a study of 14 patients at the Mayo Clinic, 6 (42%) had a history and histologic evidence of HPV infection.[5] Matoso et al.[11] evaluated a total of 29 cases of SCC of the scrotum in three North American institutions. These cases occurred between 1999 and 2013. Of 26 cases with available tissue, 7 (27%) tested positive for high-risk HPV serotypes using *in situ* hybridisation. Cases associated with HPV-infected disease displayed a predominantly basaloid or warty morphology and were characterised by p16 and Ki-67 immunostaining. Similar morphologic and immunohistochemical results in HPV-infected scrotal SCC patients suggested a similar pathogenic pathway to that proposed for penile SCC.[20] Furthermore, scrotal SCC may be a manifestation of cutaneous carcinoma risk in immunodeficient patients. Matoso et al.[11] also found that 5 out of 29 patients with SCC of the scrotum had immuno compromised conditions, such as with infection with HIV, after transplantation, and in leukaemia (Tables 1 and 2).

Table 1: Published case series with pathophysiology and management of scrotal squamous cell carcinoma.

Study	Number of patients	Design	Characteristics	Summary
Stern et al.,[6] 2002	17	Prospective multi-institutional	Cohort study, 892 men treated with PUVA	Dose-dependent increase in the risk of genital tumours in men with PUVA treatment.
Seabra et al.,[7] 2007	6	Retrospective single institution	Mean age: 52.0 years (range: 31.0–89.0)	4/6 WLE; 1/6 WLE + SLNB; 1/6 was unresectable: 1 developed LN metastasis and was treated with chemotherapy and/ or radiotherapy and subsequently died.
Wright et al.,[8] 2008	151	SEER (1973–2002)	Mean age: 68.0 years	SCC had the lowest survival rate compared to other histological subtypes.
Verhoeven et al.,[9] 2010	55	NCR (1989–2006)	Mean age: 56.5 years	SCC had the lowest survival rate compared to other histological subtypes: 5-year relative survival 77%.
Johnson et al.,[10] 2013	269	SEER (1973–2006)	Age: 65.4±14.9 years staging: LC 205	The median OS for patients with SCC was 115 (95% CI: 97–133) months.
Matoso et al.,[11] 2014	29	Retrospective, multi-institutional	Age: 55.0 years (range: 30.0–74.0) follow up: 37 months	25/29 WLE; 1/29 WLE + LND; 3/29 imiquimod post WLE. Common risk factors include HPV infection, immunocompromised states, and chronic scrotal inflammatory conditions.

DD: distant disease; LC: local disease; LN: lymph node; LND: lymphadenopathy; NCR: Netherlands Cancer Registry; OS: overall survival; PUVA: psoralens and ultraviolet A radiation; RL: regional lymph node; SCC: squamous cell carcinoma; SEER: surveillance, epidemiology and end results; SLNB: sentinel lymph node biopsy; WLE: wide local excision.

Table 2: Squamous cell carcinoma treatment outcome with pathophysiology.

SCC	Pathophysiology	Staging	Findings	Outcomes
Matoso et al.,[11] 2014 (n=29; median follow-up: 37 months)	Condylomas, other skin cancers, immunocompromised state (HIV, kidney transplantation, leukaemia/lymphoma infection/ inflammatory conditions), and tanning bed use.	*In situ* (19/29 invasive (10/29 inguinal lymph node involved (3/29)	Positive margins (13/29) recurrence (3/29)	18 NED 3 alive with disease 3 deaths not from SCC 5 No data
Andrews et al.,[5] 1991(n=14; mean follow-up: 84 months)	Psoriasis treated with coal tar and arsenic, human papillomavirus, and cutaneous epitheliomas.	Stage 1 (8/14) Stage 2 (3/14) Stage 3 (3/14)	Unknown	11 NED 3 deaths from SCC
Parys and Hutton.,[21] 1991 (n=11; median follow-up: unknown)	Industrial exposure to machine oils and tar.	Stage 1 (9/11) Stage 2 (1/11) Stage 3 (1/11)	Unknown	2 deaths from SCC

NED: No evidence of disease; SCC: squamous cell carcinoma.

Table 3: Staging scrotal cancer.

Stage	Primary tumour	Regional lymph node	Distant metastasis
0	TiS	No	M0
1	T1 = tumour size <2 cm	No	M0
2	T2 = tumour size (2–5 cm) T3 = tumour size >5 cm	No	M0
3	T4 = Deeper extra dermal structure Any T	No N1 (Regional node)	M0
4	Any T Any T	N1 Any N	M0 M1

M: metastasisation; dN: number of affected nearby lymph nodes; N: node; T: tumour; TiS: carcinoma *in situ.*

Recognised risk factors for SCC include:

- Occupations such as chimney sweeps and tar and paraffin workers. Also, occupations with exposure to mineral and cutting oils, printing, and metal working, such as car and aeroplane manufacturers, car mechanics, commercial printers, aluminum workers, shale oil workers, pitch workers, engineers, steel production workers, and cavalry personnel.
- Exposure to carcinogenic metals (e.g., arsenic, nickel, and chromium).
- Chronic mechanical irritation.
- Chronic inflammatory states (e.g., chronic lymphoedema and surgical scars).
- Lifestyle factors (e.g., poor personal hygiene and smoking).
- Viruses (e.g., HPV).
- Exposure to ionising radiation.
- Exposure to iatrogenics (e.g., coal, tar, PUVA, radiotherapy, nitrogen mustard, and Fowler's solution).
- Immunosuppression (e.g., acquired and inherited immunodeficiency, and post-transplant immunosuppression).

DISEASE STAGING

The most commonly used staging system is the Lowe modification of the system proposed by Ray and Whitmore.[22] It is based on the extent of local disease and the level of metastasis (Table 3). Diagnostic evaluation of scrotal cancer also depends on various pathologic subtypes and proper disease staging. Inguinal lymph nodes are common sites for metastasis in cases of invasive disease.

CLINICAL EXAMINATIONS OR INVESTIGATIONS

Excisional biopsy is required for the lesions to determine the histology of the scrotal cancer. Evaluation of non-localised disease and metastases can be performed through careful physical examination and cross-sectional imaging modalities, such as CT scanning or MRI; however, MRI is better for soft tissue lesion assessment. PET scanning should be considered if there is suspected pelvic lymph node involvement or beyond.[23-27]

Advanced disease may invade the testes or penis. This diagnosis is confirmed by histologic evaluation, and several areas should be sampled to determine the boundary of extension and depth of invasion. The scrotum has the same lymphatic drainage pattern as the penis. Tumours usually spread stepwise from the inguinal lymph nodes to the pelvic lymph nodes.

Interestingly, the scrotal lymphatics do not appear to cross the median raphe and drain into the ipsilateral superficial inguinal lymph nodes. Therefore, tumours without involvement of the median raphe rarely metastasise to the opposite inguinal site.[23] Because of similarities in location and histology, the clinical workup for scrotal SCC is quite similar to that of penile cancer. Routine imaging examinations include pelvic and/or abdominal CT scans and chest radiographs. Other tests, such as chest CT or PET-CT and bone scans, may be used when indicated.[23-27]

LYMPH NODE MANAGEMENT

Physical examination and cross-sectional imaging techniques are inaccurate for determining lymph node metastasis in cases of invasive scrotal SCC.[24] An inflammatory reaction may cause enlargement of the inguinal lymph nodes and fine needle aspiration cytology is the easiest way to confirm metastasis; however, the examination is only helpful if the results are positive. If the fine-needle aspiration cytology is negative and a lymph node is still palpable after antibiotic treatment, an excision biopsy is advised.[25] In cases of clinically negative inguinal nodal basin, approximately 23% of patients will harbour occult metastases.[26] However, ultrasound with fine-needle aspiration cytology reportedly failed to identify 35% of inguinal sampling with metastatic lymph nodes.[26] On the contrary, the addition of dynamic sentinel lymph node biopsy increased the detection rate to 95% and can serve as an alternative to prophylactic lymph node dissection in dedicated centres.[26] For pelvic lymph node metastases, fluorodeoxyglucose PET-CT scan reportedly showed a sensitivity of 91%, a specificity of 100%, and a diagnostic accuracy of 96% in a pilot study of 28 pelvic basins.[27,28]

MANAGEMENT AND OUTCOME

The primary treatment modality for scrotal carcinoma is surgery. Treatment for all varieties of histology requires surgical removal of the malignancy. Adjuvant treatments, including radiation therapy and chemotherapy, can be considered. Dai et al.[29] reported a case series of 10 patients with scrotal carcinoma in which all patients were treated with wide surgical excision only. After an average follow-up of 47 months, 8 patients were in good health without any recurrence. One patient developed left inguinal lymph node metastasis at 21 months that was successfully treated with bilateral inguinal lymphadenectomy, and the final patient developed bilateral pulmonary metastasis at 48 months and was palliatively treated with chemotherapy.[29] Neoadjuvant therapy (both chemotherapy and radiotherapy) has also been recommended to downstage (reduction of the tumour size and lymph node status, thus improving the stage of the disease) a very large lesion to achieve complete resection.[30,31] Adjuvant RT in combination with chemotherapy (methotrexate, bleomycin, and cisplatin) for four cycles is also recommended to achieve better disease-free survival.[32]

The prognosis in scrotal SCC depends on various factors, such as the age of the patient; size, grade, and stage of the tumour; and extent of surgery. It has been reported that the status of surgical margin is an important predictor for local and/or regional tumour control. It has also been reported that the surgical margin is still positive despite wide excision with a 2 cm margin.[33] Frozensection could have been a potential solution to this situation; however, no studies have mentioned this important diagnostic tool. Treatment outcomes of scrotal SCC in published case series are shown in Table 2.

In summary, for a patient with scrotal carcinoma and inguinal lymph node metastasis, surgical treatment followed by adjuvant chemo-radiotherapy may achieve palliative tumour control and symptom relief; however, close follow-up is warranted to evaluate long-term treatment management. The author has published a case report of a patient in whom scrotal cancer had clear blood supply from the spermatic cord. The patient was followed-up for 5 years to check for recurrence.[34]

FOLLOW-UP PLANNING

Every patient should be followed-up with history and physical examination (including skin) every 3 months for 2 years, then every 6 months for 3 years, then annually for life.[35] Patient education regarding sun protection and self-examination of the skin for regional disease recurrence needs to be mentioned during consultations.

Any recurrence should be treated by local excision. For new regional disease, regional lymph node dissection should be considered.[35] Regional recurrence or distant metastases should be reviewed and discussed in a multidisciplinary team setting for consideration of combined chemo-radiotherapy. Depending on the literature, the 5-year overall survival rates for low-risk risk scrotal cancers (sarcoma, extramammary Paget's disease, and basal cell carcinoma) and high-risk scrotal cancers (melanoma, SCC, and adnexal tumours) are about 75% and 55%, respectively.[35]

EMERGING TREATMENT

The era of targeted molecular and immuno therapies holds promise for the management of advanced SCC.[36] Cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, is now an approved agent for treatment of head and neck SCC.[37] Emerging therapies for head and neck SCC include EGFR tyrosine kinase inhibitors, vascular endothelial growth factor receptor inhibitors, insulin-like growth factor receptor inhibitors, and inhibitors of the PI3K/AKT/mTOR pathway, which may have a role in the treatment of patients with scrotal SCC in the future.[38] However, current data on the efficacy of such therapies for patients with scrotal SCC is lacking. Recently, Lavens et al.[39] showed increased EGFR expression in penile SCC. Carthon et al.[40] evaluated EGFR targeted therapy in patients with advanced penile or scrotal cancer in a retrospective case series of 24 patients. Only 1 of 24 patients had scrotal SCC. This patient developed metastases to the right groin with disease progression despite paclitaxel, ifosfamide, and cisplatin chemotherapy. The addition of EGFR-targeted therapy led to a reduction in tumour burden and thereby allowed resection of metastatic deposits. This was the only patient reported to be disease-free 38 months post EGFR therapy.[40] Further correlative-biology studies are needed to establish EGFR status in scrotal SCC tissue and response to EGFR targeted therapies in a prospective fashion. Due to the low incidence of scrotal SCC, a multicentre collaboration would be needed. Further genomic and molecular characterisation of scrotal SCC will be important in identifying key pathways and developing therapeutic targets in the future.

CONCLUSION

Although historically considered an occupational disease, the epidemiology of scrotal SCC has changed in recent years. Nowadays, iatrogenic conditions, such as PUVA and immuno suppression, and HPV infection play a significant role in the risk of developing this cancer. Surgery is the mainstay of the treatment algorithm for scrotal SCC. Excision of the primary lesion and a risk-stratified approach for the staging and treatment of regional lymph nodes is advisable. For patients with high-risk disease and negative clinical lymph nodes, sentinel lymph node biopsy can mitigate the morbidities of full groin dissection and possibly identify those with early occult disease.[24-27]

For patients with suspected pelvic node involvement, PET scanning is useful. For locally advanced and metastatic disease, palliative chemotherapy is advocated. Given the rarity of this condition, multicentre trials in conjunction with trials for the management of penile SCC are likely to provide further knowledge in this field for future urologists.

References

1. Dronsfield A. Percivall Pott, chimney sweeps and cancer. Education in Chemistry. 2006;43(2):40-2.
2. Waldron HA. A brief history of scrotal cancer. Br J Ind Med. 1983;40(4):390-401.
3. Spencer WG. Soot in cells of chimney-sweep's cancer. Med Chir Trans. 1891;74:59-68.
4. Herrel LA et al. Extramammary Paget's disease in males: Survival outcomes in 495 patients. Ann Surg Oncol. 2015;22(5):1625-30.
5. Andrews PE et al. Squamous cell carcinoma of the scrotum: Long-term follow up of 14 patients. J Urol. 1991;146(5):1299-304.
6. Stern RS et al.; PUVA Follow Up Study. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. J Am Acad Dermatol. 2002;47(1):33-9.
7. Seabra D et al. Scrotal neoplasia: Would truck drivers be at greater risk? Int Braz J Urol. 2007;33:515-9.
8. Wright JL et al. Primary scrotal cancer: Disease characteristics and increasing incidence. Urology. 2008;72(5):1139-43.
9. Verhoeven RH et al. Scrotal cancer: Incidence, survival and second primary tumours in the Netherlands since 1989. Br J Cancer. 2010;103(9):1462-6.
10. Johnson TV et al. Scrotal cancer survival is influenced by histology: A SEER study. World J Urol. 2013;31(3):585-90.
11. Matoso A et al. Squamous neoplasia of the scrotum: A series of 29 cases. Am J Surg Pathol. 2014;38(7):973-81.
12. Verhoeven RH et al. Occupation and scrotal cancer: Results of the NOCCA study. Acta Oncol. 2011;50(8):1244-6.
13. Verhoeven RH et al. New insights into the aetiology of scrotal cancer, a nationwide case-control study in the Netherlands. J Eur Acad Dermatol Venereol. 2014;28(1):65-71.
14. Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. The Photochemotherapy Follow-up Study. N Engl J Med. 1990;322(16):1093-7.
15. Henseler T et al. Skin tumors in the European PUVA Study. Eight-year follow-up of 1,643 patients treated with PUVA for psoriasis. J Am Acad Dermatol. 1987;16(1 Pt 1):108-16.
16. Lindelöf B et al. PUVA and cancer risk: The Swedish follow-up study. Br J Dermatol. 1999;141(1):108-12.
17. Hannuksela-Svahn A et al. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol. 2000;114(3):587-90.
18. Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. Toxicol Appl Pharmacol. 2004;195(3):298-308.
19. Archier E et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: A systematic literature review. J Eur Acad Dermatol Venereol. 2012;26(Suppl 3):22-31.
20. Ferreux E et al. Evidence for at least three alternative mechanisms targeting the p16INK4A/cyclin D/Rb pathway in penile carcinoma, one of which is mediated by high-risk human papillomavirus. J Pathol. 2003;201(1):109-18.
21. Parys BT, Hutton JL. Fifteen-year experience of carcinoma of the scrotum. Br J Urol. 1991;68(4):414-7.
22. Lowe FC. Squamous cell carcinoma of the scrotum. J Urol. 1983;130(3):423-7.
23. Chung BI et al., "Surgical, radiology, and endoscopic anatomy of the male pelvis," Wein AJ et al. (eds.), Campbell-Walsh Urology (2015) 10th edition, volume 3, Philadelphia: Elsevier, pp.1630.
24. Hughes B et al. Non-invasive and minimally invasive staging of regional lymph nodes in penile cancer. World J Urol. 2009;27(2):197-203.
25. Zhu Y et al. Development and evaluation of a nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes. J Urol. 2010;184(2):539-45.
26. Lam W et al. Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: A prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. Eur Urol. 2013;63(4):657-63.
27. Graafland NM et al. Scanning with 18F-FDG-PET/CT for detection of pelvic nodal involvement in inguinal node-positive penile carcinoma. Eur Urol. 2009;56(2):339-45.
28. Zhu Y et al. Preneoplastic and primary scrotal cancer: Updates on pathogenesis and diagnostic evaluation. Urol Clin North Am. 2016;43(4):523-30.
29. Dai B et al. Basal cell carcinoma of the scrotum: Clinicopathologic analysis of 10 cases. Dermatol Surg. 2012;38(5):783-90.
30. Friedman R et al. Squamous cell carcinoma arising in a Leishmania scar. Dermatol Surg. 2003;29(11):1148-9.
31. Harder Y et al. Squamous cell carcinoma of the penile skin in a neovagina 20 years after male-to-female reassignment. Br J Plast Surg. 2002;55(5):449-51.
32. Arai Y et al. [A case of scrotal cancer with inguinal lymph node metastasis treated by multidisciplinary modalities including chemotherapy with methotrexate, bleomycin and cisplatin]. Hinyokika Kiyo. 1997;43(9):683-5. (In Japanese).
33. Ng LG et al. Extramammary Paget's disease of scrotum. Urology. 2001;58(1):105.
34. Sarkar D, Parr NJ. Unusual presentation of a scrotal tumour. BMJ Case Rep. 2014;2014.
35. Huang JH et al. Surgical management of primary scrotal cancer. Urol Clin North Am. 2016;43(4):531-44.
36. Vyas R et al. Squamous cell carcinoma of the scrotum: A look beyond the chimneystacks. World J Clin Cases. 2014;2(11):654-60.
37. Cohen RB. Current challenges and clinical investigations of epidermal growth factor receptor (EGFR)- and ErbB family targeted agents in the treatment of head and neck squamous cell carcinoma (HNSCC). Cancer Treat Rev. 2014;40(4):567-77.
38. Dorsey K, Agulnik M. Promising new molecular targeted therapies in head and neck cancer. Drugs. 2013;73(4):315-25.
39. Lavens N et al. EGFR overexpression in squamous cell carcinoma of the penis. Curr Oncol. 2010;17(1):4-6.
40. Carthon BC et al. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. BJU Int. 2014;113(6):871-7.

The Evaluation and Management of Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Interstitial cystitis or bladder pain syndrome is a frustrating symptom complex for both the patient and the clinician. Classic Hunner's lesion interstitial cystitis is clearly a bladder disease and treating the bladder improves symptoms. Non-Hunner's lesion interstitial cystitis or bladder pain syndrome likely has multiple aetiologies and in many cases the bladder is an innocent bystander in a bigger pelvic process. For many years, non-Hunner's lesion interstitial cystitis has been treated with bladder-directed therapies, with poor overall outcomes. This literature review article will review the diagnosis and management of interstitial cystitis and encourage the reader to look beyond the bladder to achieve symptom relief.

INTRODUCTION

Since interstitial cystitis was originally defined in 1887,[1] the nomenclature has shifted following further discoveries about the disease and its association with other issues outside the bladder. There is no definitive marker to diagnose interstitial cystitis, or bladder pain syndrome (IC/BPS), but diagnosis is symptom driven. The authors adopt the definition of IC/BPS from the Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU), which states that IC/BPS is: "an unpleasant sensation (pain, pressure, and/or discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of >6 weeks duration, in the absence of infection or other identifiable causes."[2] The authors further subcategorise patients into non-Hunner's lesions (HL) interstitial cystitis (N-HLIC/BPS) and HLIC. HLIC is a bladder disease with relatively straightforward treatment. N-HLIC/BPS is a syndrome requiring a multimodal approach that is tailored to individual patients.

Over time, the diagnosis of IC/BPS was oversimplified and patients that feel pain from their umbilicus to their knees were labelled with IC based on a validated questionnaire or a potassium sensitivity test. Unfortunately, this simplification failed to confirm whether the bladder was driving the symptoms. Many of these patients would see multiple healthcare

professionals and trial numerous treatments without benefit.[3] It is now clear that clinicians must be astute, evaluate triggers that can impact the patient's symptoms, and use a multimodal approach to improve quality of life.

COMPREHENSIVE EVALUATION

A careful history and physical exam are critical in patients with symptoms of IC/BPS. These patients commonly have systemic comorbidities or symptom complexes, such as depression, fibromyalgia, chronic fatigue syndrome, Sjögren's syndrome, endometriosis, inflammatory bowel disease, migraines, and temporomandibular joint disorder.[4] Furthermore, a systemic disease manifesting in the bladder may present as IC/BPS.

IC/BPS patients often present with urinary urgency and frequency and pelvic discomfort. Pelvic pain is usually worse with bladder filling and is relieved following voiding. Multiple pain triggers are found in patients labelled with IC/BPS, making treatment difficult. In a study of 193 IC/BPS patients, 73% reported pain sites outside the bladder or pelvic area, with those patients also experiencing more severe pain and depression.[5] Evaluating the pelvic floor muscles during a pelvic exam is crucial. Pelvic floor dysfunction (PFD) and myofascial pain are found in up to 87% of patients diagnosed with IC/BPS.[6] A study comparing MRI of women with IC/BPS to age-matched controls identified hypertonicity of the pelvic floor.[7] A tight pelvic floor can refer pain to the pelvis, vulva, rectum, or perineum and result in obstructed voiding, leading to urinary hesitancy, urgency, and frequency.[3]

Pudendal neuropathy can be associated with symptoms of IC/BPS. Clinicians can identify IC/BPS by using the Nantes criteria: pain in the anatomical territory of the pudendal nerve, worsened by sitting, not causing patient to be woken at night, no objective sensory loss, and positive anaesthetic pudendal nerve block.[8] Vulvodynia is the fourth most common IC-associated syndrome, affecting up to 48% of IC/BPS patients.[9] Vulvodynia is a superficial pain, often localised to the opening of the vagina, triggered during penetration or with light touch.

Sexual dysfunction occurs frequently in IC/BPS patients and decreases their quality of life.[10] Patients should be specifically questioned about dyspareunia, vaginal dryness, orgasmic dysfunction, and sexual desire. Dyspareunia is often caused by PFD, but frequently vestibulodynia contributes to the condition.

Furthermore, anticipation of pain during intercourse increases pelvic floor tone, creating a pain cycle that is difficult to break. A full social history, including previous abuse (emotional, physical, or sexual), should be recorded. Many patients with IC/BPS have a history of abuse, which may be associated with more pain and fewer voiding problems.[4]

Gastrointestinal symptoms should be evaluated and treated. Bowel complaints are often associated with lower urinary tract symptoms, likely secondary to neural crosstalk of the pelvic organs.[11] Chronic constipation is a common issue in patients with IC/BPS, which may be caused by their underlying PFD or secondary to medications, such as opioids or antimuscarinics.[3]

Voiding diaries can be filled out by patients to quantify urinary symptoms.[2] Validated questionnaires are commonly used to quantify symptoms and assess changes during treatment, but questionnaires should not be used alone for the diagnosis of IC/BPS. The Interstitial Cystitis Symptom Index and Problem Index can show changes in symptoms over time.[12] Urodynamic studies can aid the diagnosis of patients with bladder outlet obstruction.

Urinalysis and urine culture must be checked to screen for infection or microscopic haematuria. Haematuria increases the suspicion of HLIC or another urological pathology and should prompt cystoscopy to visually evaluate the bladder and urine cytology to screen for cancer. If HL are identified, treatment should focus on these lesions first. Urothelial cancer can be a source of irritative voiding symptoms. A study of 600 patients treated for IC/BPS found that 1% of patients had urothelial cancer as the source of their irritative voiding symptoms, which resolved after treating the malignancy.[13] Furthermore, patients with IC/BPS may be at higher risk of subsequently developing urothelial cancer according to a recent nationwide population-based study.[14]

NON-HUNNER'S LESION INTERSTITIAL CYSTITIS OR BLADDER PAIN SYNDROME

Treatment options are variable for IC/BPS but should focus on identified pain triggers, such as PFD. Given the complexity of IC/BPS, a multidisciplinary clinic is the most effective way to treat this patient population. The authors lead a clinic that involves urologists, gynaecologists, pelvic floor physical therapists, colorectal surgeons, integrative specialists, and pain psychologists who communicate together to tailor a multimodal therapy for each individual. A multidisciplinary clinic is extremely successful in managing IC/BPS patients, with very high patient satisfaction.[3]

Behavioural Modifications and Stress Management

All patients should be offered first-line therapy with behaviour modifications, including an elimination diet to identify any food triggers. Most patients will report that stress flares their symptoms. Stress management is a crucial component to the multidisciplinary care of IC/BPS patients. Pain psychologists can address past and present life stressors and provide coping strategies to the chronic pain patient. Cognitive behavioural therapy can help patients develop coping strategies. Interpersonal therapy may help patients work through intimacy related issues. Emotionally expressive therapy may help address painful experiences prior to onset of their symptoms.[4]

Complementary therapies, including acupuncture, massage, guided imagery, and reiki, focus on the mind–body connection and may have a role in the treatment of IC/BPS. A recent systematic review of randomised control trials investigating acupuncture treatment of chronic pelvic pain in women found that acupuncture in combination with conventional treatment significantly reduced pelvic pain.[15] Although there is a lack of robust clinical trials investigating complementary therapies, it is the authors' experience that they can be very helpful in managing symptoms of IC/BPS.

Oral and Intravesical Therapies

The American Urological Association (AUA) guidelines detail a list of optional second-line treatments for IC/BPS, including oral medications and intravesical therapies.[2] In the authors' experience, these may only be effective in a subset of patients with true bladder centric symptoms without HLIC.

Pentosan polysulfate (PPS) is a U.S. Food and Drug Administration (FDA) approved and is believed to help repair damage to the glycosaminoglycan layer of the bladder. In 1987, a randomised, multicentre, double-blinded, placebo-controlled study reported significant success with PPS.[16] Over time, its efficacy has been questioned and a recent dose-ranging, placebo-controlled study revealed no significant difference between groups.[17] In addition, there is recent concern about the development of pigmentary maculopathy following prolonged use of PPS.[18] In the authors' opinion, given its limited efficacy, cost, and potential complications, PPS should be used with caution and with clear informed consent.

Cimetidine and hydroxyzine are thought to affect mast cell degranulation in the bladder wall. A prospective, randomised, placebo-controlled study of cimetidine was very effective in relieving symptoms.[19] A subsequent multicentre randomised controlled trial compared hydroxyzine with oral PPS and reported that neither provided benefit to patients with IC.[20] Amitriptyline in combination with education and behavioural modification did not significantly improve IC/BPS symptoms compared to placebo, but with dose-escalation to ≥50 mg there was a significantly higher response rate.[21] Despite lack of strong evidence, trials of cimetidine, hydroxyzine, and amitriptyline can be offered, but should be discontinued if there is lack of improvement.

Patients with symptoms of IC/BPS often use over the counter 'nutraceuticals', with ingredients such as aloe vera, quercetin, and calcium glycerophosphate. Although there may be benefits from some of these ingredients, the data are sparse. The authors often partner with naturopathic physicians to help guide patients on their supplement choices.

Intravesical dimethyl sulfoxide (DMSO) therapy is FDA approved and believed to provide anti-inflammatory, analgesic, and muscle relaxant properties. A literature review detailing

the impact of DMSO on IC/BPS revealed a lack of standardisation with short-term follow-up and suggested the importance of discovering potential biomarkers to subtype the precise patient for its use.[22] Other therapy cocktails combine DMSO with heparin, lidocaine, sodium bicarbonate, intravesical PPS, chondroitin sulfate, and hyaluronic acid, and the guidelines recommend individualisation for each patient.[2]

Pelvic Floor Physical Therapy

Pelvic floor physical therapy (PFPT) is a second-line treatment detailed in the AUA guidelines.[2] Physical therapists must be specially trained to perform intravaginal myofascial release; the therapy also involves the manipulation of the patient's external trunk and lower extremities. Treating the tenderness and tightness of the pelvic floor musculature can indirectly improve associated urinary, bowel, and sexual symptoms.[4] The benefit of PFPT has been demonstrated in many studies, including a National Institutes of Health (NIH) sponsored trial that compared PFPT with internal pelvic muscle work against general therapeutic massage.[23-26] In the authors' experience, most patients diagnosed with IC/BPS actually have PFD as the cause of their symptoms, and PFPT is a highly effective treatment pathway.

Trigger Point Injections

Trigger point injections (TPI) have been shown to improve pelvic pain. A study of 18 women showed that 72% had significant improvement of pain and 33% were pain free after their first TPI.[27] A cadaver study using a systematic standard template characterised the pelvic floor muscle injections and confirmed the ability to successfully deliver medications to the pelvic floor.[28] The authors use the aforementioned template with long-acting local anaesthetic for immediate relief and a corticosteroid for sustained relief. TPI are often used as an adjunct to PFPT. Most women tolerate a transvaginal approach in the office. Men with pelvic pain can have TPI carried out transrectally or through the perineum. One study of men with chronic pelvic pain syndrome reported improvement in about half of patients after TPI as an adjunct to PFPT.[29] Botulinum toxin is also being studied for injection into the pelvic floor for longer-term relief. Single and repeat injections both show significant reduction in pelvic pain.[30] A study of 28 women with pelvic pain and IC/BPS or vulvodynia who underwent injection of 300 units of botulinum toxin reported improvement in 80% of patients at 24 weeks;[31] however, further evaluation is warranted.

Pudendal Nerve Blocks

Patients with PFD commonly present with symptoms of pudendal neuralgia. Pudendal nerve blocks can be completed with or without trigger point injections. They can be carried out transvaginally or transgluteally. Improvement in pain after a pudendal nerve block suggests that the pudendal nerve is involved in the pain process. A series of pudendal nerve blocks with multidisciplinary treatments significantly improve patients' symptoms.[3]

Intravaginal Medications

Local intravaginal medications, such as diazepam or baclofen, are used to manage IC/BPS symptoms. A study that evaluated treatment with vaginal diazepam reported 62% of patients demonstrated significant improvements in pain after one month.[32] In a different study of women with hypertonic pelvic floor muscles on exam and electromyography reported no improvement in subjective outcomes or electromyography following vaginal diazepam versus placebo.[33] Vaginal diazepam has been reported in another study to significantly improve pain and pelvic floor function when used as an adjuvant therapy to PFPT and TPI.[34] Vulvodynia has been successfully treated with an analgesic cream containing baclofen and palmitoylethanolamide, an endogenous anti-inflammatory compound.[34]

OnabotulinumtoxinA

The AUA guidelines list intravesical OnabotulinumtoxinA (Botox) injections as a fourth-line treatment for IC/BPS. Originally cited to relieve urgency and frequency, Botox may cause peripheral afferent desensitisation providing additional pain relief.[35] Literature reviews, including a recent meta-analysis, revealed that Botox consistently reduced morbidity, including a reduction in pelvic pain, urinary frequency, nocturia, and improved quality of life and bladder capacity.[36,37] The authors offer intravesical Botox injections to relieve urgency and frequency but

only to patients who understand the risk of urinary retention.

Neuromodulation

Sacral neuromodulation for chronic pelvic pain is still considered experimental.[38] Sacral neuromodulation is FDA approved for the management of urge incontinence, faecal incontinence, and frequency-urgency syndrome, but it is not approved to treat pain caused by IC/BPS. Studies have shown sacral neuromodulation to be safe and efficacious over long treatment durations with the ability to alleviate pain and decrease narcotic medication use in refractory IC patients.[39-41] A meta-analysis of sacral neuromodulation for refractory IC patients reported a pooled overall success of 84% with improvement in pelvic pain, daytime frequency, nocturia, urgency, and average voiding volumes.[42] Pudendal neuromodulation has shown excellent results for patients with N-HLIC/BPS and pudendal neuralgia.[43-45] In a series of patients with pudendal pain, all had an improvement in pain, including six patients who had previously failed to respond to sacral neuromodulation.[44] A new implantable electrode with an external energy source (StimWave, Inc., Pompano Beach, Florida, USA) is approved for peripheral nerve pain, including action on the pudendal nerve. This allows clinicians to offer neuromodulation for patients with only pain and not voiding or bowel dysfunction.

Percutaneous tibial nerve stimulation has been shown to improve pelvic pain in medication-refractory patients. Specific studies for treating IC/BPS have reported conflicting results and further studies are needed.[38] Central, supraspinal modulation through brain stimulation may also benefit pelvic pain patients, specifically patients who have failed peripheral approaches, and has shown success in case reports, but additional studies are indicated.[38]

HUNNER'S LESION INTERSTITIAL CYSTITIS

The presence of HL on cystoscopy is the key to distinguishing HLIC from N-HLIC/BPS. HL represent an inflamed vulnerable area of the bladder and appear as circumscribed, reddened mucosal areas with small vessels radiating towards a central scar.[46] HLIC is rarer, representing roughly 10–15% of IC/BPS patients, and occurs through a separate disease process.[3] A recent prospective trial of IC/BPS patients reported there is no distinct clinical phenotype to differentiate HLIC, suggesting that cystoscopy be conducted in all patients with IC/BPS to rule out HL.[47] HLIC patients are generally older, have a rapid onset of symptoms with more severe urinary frequency, and a decreased bladder capacity.[4] HL may be more commonly found in male patients with IC/BPS.[48] HLIC patients have fewer comorbidities and less systemic involvement compared to N-HLIC/BPS.[49]

First-Line Therapy

Dietary modification has been shown to reduce symptoms and improve quality of life within 3 months with continued efficacy for 1 year.[50] The specifically designed diet avoided tomatoes, spices, citrus, soybeans, and additional foodstuffs. In the author's experience, elimination diets are effective in a motivated patient, but are too cumbersome for most to adhere to. Diluting the toxins in the urine by increasing water intake can help patients with HLIC.

Cystoscopic Treatment

AUA guidelines list hydrodistension (HD) as a third-line option for IC/BPS when other treatments have failed and recommend it be conducted under anaesthesia for <10 minutes with pressures around 60–80 cm H_2O.[2] Previously, HD was used to identify glomerulations that were thought to be pathognomonic for IC/BPS, but the presence or absence of glomerulations is nonspecific, so the only role of HD is to improve symptoms.[2] HD has been tried in up to 85% of patients with a diagnosis of IC/BPS.[51] Although it is a popular intervention, there is weak evidence to support its effectiveness.[52] In total, <20% of patients report excellent improvement after HD with mostly short-lived relief of <6 months.[4]

In the authors' practice, HD is performed to determine the anaesthetic bladder capacity as a prognostic variable and aid in electrocautery of HL, since the lesions split and crack, to define the true borders of the HL.[46] According to the guidelines, if HL are present, fulguration should be performed with laser or electrocautery.[2] The authors always perform a biopsy of a HL to rule

out carcinoma *in situ* and then use a roller ball on a resectoscope and rapidly fulgurate over the lesions to avoid a deep burn. Electrocautery has been shown to provide symptom improvement in many studies although the durability is variable. Many patients with fulguration alone will have recurrent symptomatic HL requiring repeat electrocautery.[53-55] A long-term study of 76 patients who underwent a total of 214 electrocautery procedures for HL had significant improvement in pain, urgency, and frequency. Overall, 89.6% of patients noted some degree of symptom improvement, 56.3% noted a marked improvement, and 84.0% of patients reported electrocautery as the most beneficial treatment they received. The study also showed that there was no reduction in bladder capacity after single or multiple electrocautery treatments.[56] A retrospective review of patients who underwent their first HD with fulguration found that the extent of HL is associated with symptom severity and bladder capacity but did not predict the need for a repeat HD.[57]

Injection of a corticosteroid into the HL at time of fulguration is an optional treatment according to AUA guidelines.[2] One study of HLIC patients who received a total dose of 400 mg of triamcinolone reported symptom improvement in 70% with an average duration of 7–12 months.[58] There are no substantial safety data for a 400 mg dose, so it is recommended to limit the total dose to 60 mg.[2]

Medical Treatment

Cyclosporine A is an immunosuppressive agent used to suppress bladder inflammation in IC/BPS and is listed as a fifth-line treatment in the AUA guidelines.[2] Excellent outcomes have been reported for cyclosporine in IC/BPS, including superiority to PPS.[59-61] HLIC patients are more likely to benefit from cyclosporine.[62] Following electrocautery, the authors routinely prescribe cyclosporine for patients with recurrent HL at a starting dose of 100 mg twice daily for 30 days followed by 100 mg once daily. The dose for IC/BPS is low, thus limiting toxicity, but monitoring blood pressure and renal function is necessary. A recent study monitored cyclosporine concentration in patients 2 hours after drug administration, creatinine, and blood pressure to effectively minimise toxicity. The cyclosporine concentration ranged widely, with no correlation to treatment response, but was a useful tool to reduce the dose and minimise toxicity.[62]

Reconstructive Surgery

When all other therapies have failed, substitution cystoplasty or urinary diversion with or without cystectomy is an option according to the AUA guidelines.[2] Reconstructive surgery resulted in symptom resolution in 82% of patients with HLIC, but this surgery only benefited 23% of patients with N-HLIC/BPS.[63] A long-term, retrospective review of IC/BPS patients who underwent major surgery reported good symptom relief for those with disabling symptoms and that extended preoperative duration of symptoms may increase risk of persistent pain after surgery.[64] Another study found that augmentation with supratrigonal cystectomy significantly improved symptoms and increased bladder capacity in HLIC patients.[65] Reconstructive surgery can potentially benefit refractory HLIC patients; however, the patients should understand the risks of irreversible major surgery with associated lifelong changes and possibility of persistent pain.[2] An IC/BPS specialist should evaluate patients prior to considering surgery. According to the literature, the best response will be in patients with a small bladder capacity under anaesthesia and with an absence of neuropathic pain.[2] This treatment is not recommended for N-HLIC/BPS patients.

BIOMARKERS

No clear pathophysiologic explanation of IC/BPS has been determined, but some proposed mechanisms focus on the dysfunction of the bladder epithelium, extracellular matrix, and associated immune mediators. These cellular processes have been linked to specific chemical biomarkers in the urine, serum, and stool.[66,67] More recently, proteomics of urine have identified a number of proteins associated with IC/BPS and a pattern of protein expression to differentiate patients with IC/BPS from asymptomatic controls.[68] To date, no biomarker has shown adequate sensitivity and specificity to provide diagnostic assistance yet, they offer the potential to differentiate between systemic and focal disorders or subclassify patients into specific phenotypes, which may allow for a more targeted treatment approach.

CONCLUSION

IC/BPS is a challenging symptom complex for the clinician to manage. Many patients are overwhelmed and burdened by the disease, especially after failing therapies directed at their bladders. HLIC is a bladder disease, responds to bladder directed therapy, and should be considered a separate disease from N-HLIC/BPS. A multidisciplinary approach is crucial for success in treating N-HLIC/BPS. It is critical to carefully phenotype these patients, identify pain triggers, and direct therapy towards these triggers. A hypertonic pelvic floor is often overlooked during the evaluation of a patient with symptoms suggestive of IC/BPS. In the authors' opinion, identifying and treating PFD with physical therapy, trigger point injections, pudendal nerve blocks, integrative medicine treatments, psychological support, and neuromodulation offer the best success in the management of the refractory IC/BPS patient.

The bladder is often an innocent bystander in a bigger pelvic process. It is time to think beyond the bladder!

References

1. Skene AJC, Diseases of the bladder and urethra in women (1887), New York: William Wood and Company, pp. 374.
2. Hanno PM et al. Diagnosis and treatment of interstitial cystitis/ bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193(5):1545-53.
3. Gupta P et al. A multidisciplinary approach to the evaluation and management of interstitial cystitis/ bladder pain syndrome: An ideal model of care. Transl Androl Urol. 2015;4(6):611-9.
4. Han E et al. Current best practice management of interstitial cystitis/ bladder pain syndrome. Ther Adv Urol. 2018;10(7):197-211.
5. Tripp DA et al. Mapping of pain phenotypes in female patients with bladder pain syndrome/interstitial cystitis and controls. Eur Urol. 2012;62(6):1188-94.
6. Peters KM et al. Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. Urology. 2007;70(1):16-8.
7. Ackerman AL et al. MRI suggests increased tonicity of the levator ani in women with interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2016;27(1):77-83.
8. Labat JJ et al. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn. 2008;27(4):306-10.
9. Carrico DJ et al. The relationship of interstitial cystitis/painful bladder syndrome to vulvodynia. Urol Nurs. 2009;29(4):233-8.
10. Tonyali S, Yilmaz M. Sexual dysfunction in interstitial cystitis. Curr Urol. 2017;11(1):1-3.
11. Minagawa T et al. Mechanisms of pelvic organ cross-talk: 2. Impact of colorectal distention on afferent nerve activity of the rat bladder. J Urol. 2013;190(3):1123-30.
12. O'Leary MP et al. The interstitial cystitis symptom index and problem index. Urology. 1997;49(5A; Suppl 1):58-63.
13. Tissot WD et al. A referral center's experience with transitional cell carcinoma misdiagnosed as interstitial cystitis. J Urol. 2007;172(2):478-80.
14. Wu MP et al. Risk of urinary tract carcinoma among subjects with bladder pain syndrome/Interstitial cystitis: A nationwide population-based study. Biomed Res Int. 2018:7495081.
15. Sung SH et al. Acupuncture treatment for chronic pelvic pain in women: A systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2018:9415897.
16. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. J Urol. 1987;138(3):513-6.
17. Nickel JC et al. Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: Insights from a randomized, double-blind, placebo controlled study. J Urol. 2015;193(3):857-62.
18. Pearce WA et al. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. Ophthalmology. 2018;125(11):1793-802.
19. Thilagarajah R et al. Oral cimetidine gives effective symptom relief in painful bladder disease: A prospective, randomized, double-blind placebo-controlled trial. BJU Int. 2001;87(3):207-12.
20. Sant GR et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol. 2003;170(3):810-5.
21. Foster HE et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/ painful bladder syndrome. J Urol. 2010;183(5):1853-8.
22. Rawls WF et al. Dimethyl sulfoxide (DMSO) as intravesical therapy for interstitial cystitis/bladder pain syndrome: A review. Neurourol Urodyn. 2017;36(7):1677-84.
23. Weiss JM. Pelvic floor myofascial trigger points: Manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol. 2001;166(6):2226-31.
24. Fitzgerald MP et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol. 2012;187(6):2113-8.
25. Fitzgerald MP et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol. 2009;182(2):570-80.
26. Bedaiwy MA et al. Prevalence of myofascial chronic pelvic pain and the effectiveness of pelvic floor physical therapy. J Reprod Med. 2013;58(11-12):504-10.
27. Langford CF et al. Levator ani trigger point injections: An underutilized treatment for chronic pelvic pain. Neurourol Urodyn. 2007;26(1):59-62.
28. Gupta P et al. Transvaginal pelvic floor muscle injection technique: A cadaver study. Female Pelvic Med Reconstr Surg. 2017;23(1):61-3.
29. Tadros NN et al. Utility of trigger point injection as an adjunct to physical therapy in men with

chronic prostatitis/chronic pelvic pain syndrome. Transl Androl Urol. 2017;6(3):534-7.

30. Nesbitt-Hawes EM et al. Improvement in pelvic pain with botulinum toxin type A - Single vs. repeat injections. Toxicon. 2013;63:83-7.
31. Morrissey D et al. Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high-tone pelvic floor dysfunction: A 6-month prospective pilot study. Female Pelvic Med Reconstr Surg. 2015;21(5):277-82.
32. Carrico DJ, Peters KM. Vaginal diazepam use with urogenital pain/pelvic floor dysfunction: Serum diazepam levels and efficacy data. Urol Nurs. 2011;31(5):279-84.
33. Crisp CC et al. Intra-vaginal diazepam for high-tone pelvic floor dysfunction: A randomized placebo-controlled trial. Int Urogynecol J. 2013;24(11):1915-23.
34. Rogalski MJ et al. Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. Int Urogynecol J. 2010;21(7):895-9.
35. Shie JH et al. Immunohistochemical evidence suggests repeated intravesical application of botulinum toxin A injections may improve treatment efficacy of interstitial cystitis/bladder pain syndrome. BJU Int. 2013;111(4):638-46.
36. Hanno PM et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185(6):2162-70.
37. Wang CC et al. Efficacy and safety of intravesical onabotulinumtoxin-A injection in patients with detrusor hyperactivity and impaired contractility. Toxins (Basel). 2016;8(3):82.
38. Roy H et al. Neuromodulation for pelvic and urogenital pain. Brain Sci. 2018;8(10):180.
39. Valovska A et al. Sacral neuromodulation as a treatment for pudendal neuralgia. Pain Physician. 2014;17(5):645-50.
40. Peters KM, Konstandt D. Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int. 2004;93(6):777-9.
41. Gajewski JB, Al-Zahrani AA. The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. BJU Int. 2011;107(8):1258-64.
42. Wang J et al. Sacral neuromodulation for refractory bladder pain syndrome/Interstitial cystitis: A global systematic review and meta-analysis. Sci Rep. 2017;7(1):11031.
43. Peters KM et al. Chronic pudendal neuromodulation: Expanding available treatment options for refractory urologic symptoms. Neurourol Urodyn. 2010;29(7):1267-71.
44. Peters KM et al. Pilot study exploring chronic pudendal neuromodulation as a treatment option for pain associated with pudendal neuralgia. Low Urin Tract Symptoms. 2015;7(3):138-42.
45. Heinze K et al. Comparative pilot study of implantation techniques for pudendal neuromodulation: Technical and clinical outcome in first 20 patients with chronic pelvic pain. World J Urol. 2015;33(2):289-94.
46. Fall M et al. Chronic interstitial cystitis: A heterogeneous syndrome. J Urol. 1987;137(1):35-8.
47. Doiron RC et al. Clinical phenotyping does not differentiate Hunner lesion subtype of interstitial cystitis/bladder pain syndrome: A relook at the role of cystoscopy. J Urol. 2016;196(4):1136-40.
48. Forrest JB, Schmidt S. Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: A common and frequently identical clinical entity. J Urol. 2004;172(6):2561-2.
49. Peters KM et al. Are ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome 2 distinct diseases? A study of coexisting conditions. Urology. 2011;78(2):301-8.
50. Oh-Oka H. Clinical efficacy of 1-year intensive systematic dietary manipulation as complementary and alternative medicine therapies on female patients with interstitial cystitis/bladder pain syndrome. Urology. 2017;106:50-54.
51. Peters KM, Carrico DJ. Frequency, urgency, and pelvic pain: Treating the pelvic floor versus the epithelium. Curr Urol Rep. 2006;7(6):450-5.
52. Olson LE et al. A systematic review of the literature on cystodistension in bladder pain syndrome. Int Urogynecol J. 2018;29(2):251-7.
53. Payne RA et al. Endoscopic ablation of Hunner's lesions in interstitial cystitis patients. Can Urol Assoc J. 2009;3(6):473-7.
54. Lee ES et al. Effect of transurethral resection with hydrodistention for the treatment of ulcerative interstitial cystitis. Korean J Urol. 2013;52(10):682-8.
55. Hillelsohn JH et al. Fulguration for Hunner ulcers: Long-term clinical outcomes. J Urol. 2012;188(6):2238-41.
56. Chennamsetty A et al. Electrosurgical management of Hunner ulcers in a referral center's interstitial cystitis population. Urology. 2015;85(1):74-8.
57. Akiyama Y et al. Extent of Hunner lesions: The relationships with symptom severity and clinical parameters in Hunner type interstitial cystitis patients. Neurourol Urodyn. 2018;37(4):1441-7.
58. Cox M et al. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. Can J Urol. 2009;16(2):4536-40.
59. Forrest JB et al. Cyclosporine A for refractory interstitial cystitis/bladder pain syndrome: Experience of 3 tertiary centers. J Urol. 2012;188(4):1186-91.
60. Ehren I et al. Nitric oxide as a marker for evaluation of treatment effect of cyclosporine A in patients with bladder pain syndrome/interstitial cystitis type 3C. Scand J Urol. 2013;47(6):503-8.
61. Sairanen J et al. Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: A randomized comparative study. J Urol. 2005;174(6):2235-8.
62. Crescenze IM et al. Efficacy, side effects, and monitoring of oral cyclosporine in interstitial cystitis-bladder pain syndrome. Urology. 2017;107:49-54.
63. Rössberger J et al. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: Subtyping is imperative. Urology. 2007;70(4):638-42.
64. Andersen AV et al. Long-term experience with surgical treatment of selected patients with bladder pain syndrome/interstitial cystitis. Scand J Urol Nephrol. 2012;46(4):284-9.
65. Kim HJ et al. Efficacy and safety of augmentation ileocystoplasty combined with supratrigonal cystectomy for the treatment of refractory bladder pain syndrome/interstitial cystitis with Hunner's lesion. Int J Urol. 2014;21 (Suppl 1):69-73.
66. Patnaik SS et al. Etiology, pathophysiology and biomarkers of interstitial cystitis/painful bladder syndrome. Arch Gynecol Obstet. 2017;295(6):1341-59.
67. Keay S et al. Antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor in men with interstitial cystitis versus chronic pelvic pain syndrome. Urology. 2004;63(1):22-6.
68. Canter MP et al. Proteomic techniques identify urine proteins that differentiate patients with interstitial cystitis from asymptomatic control subjects. Am J Obstet Gynecol. 2008;198(5):553.e1-6.

Fracture of the Penis: A Review

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Abstract

Fracture of the penis is not uncommon and usually occurs during intercourse when the erect penis forcefully hits against the perineum or symphysis pubis. The aetiology varies with geographical area, and additionally penile self-manipulation is more common in the Middle East. While imaging may be used as an adjunct to aid diagnosis, especially in equivocal cases, it remains largely a clinical diagnosis. Immediate repair has been established as the standard of care although delayed repair has also been employed with equally successful outcomes. The degloving incision facilitates very good exposure but repair may be undertaken via a simple direct incision if the fracture site can be localised. Urethral injuries usually require repair, although successful non-operative management of small partial tears has been described. Postoperative medications to suppress erections have not been of proven benefit.

Penile fracture may be defined as traumatic disruption of the tunica albuginea and enclosed corpus cavernosum as a result of blunt trauma to the erect penis. It may involve the corpus spongiosum and the urethra.[1,2] The aetiology of penile fracture varies with geographical area. In the Western hemisphere vaginal intercourse accounts for most cases of penile fracture.[3] Reports from Japan indicate that only 19% of their cases result from sexual intercourse, with other aetiologic factors being masturbation and rolling over in bed onto an erect penis. Penile fracture during intercourse occurs as the result of the erect penis forcefully hitting against the perineum or symphysis pubis. In one large series from the Middle East, more than three-quarters of the reported cases of fractured penis were as a result of manually bending the erect penis to achieve detumescence, a practice known as Taqaandan.[4] However, in another Iranian study of 620 men, most cases (56%) were due to sexual intercourse, followed by non-intercourse trauma and masturbation in 24% and 17%, respectively.[5] Other much rarer causes of penile fractures include placing the erect penis in tight clothing, falling from a height onto the penis, animal bites of the erect penis, and entrapment of the erect penis in bamboo beds, although the veracity of these accounts can never be verified.[6-8]

The tunica albuginea is a tough fascial layer which envelops the penis. One of the toughest fascias, the albuginea is normally about 2 mm thick but thins out during erection to about

0.25–0.50 mm and loses its elasticity.[9] It has been estimated that the intracorporeal pressure required to rupture the tunica is in the region of 1,500 mmHg, which far exceeds the 100 mmHg that is the normal intracorporeal pressure during an erection.[10] During acute loading, usually via angulation of the erect penis, the intracavernous pressure may increase to such an extent as to cause rupture of the tunica. Cavernosal blood leaks into surrounding tissues and may remain confined to the penis if Buck's fascia is intact or, if Buck's fascia is ruptured, blood extravasates around Colles' fascia creating a 'butterfly' ecchymosis in the scrotum and perineum.[11]

Albugineal rupture is mostly unilateral, transverse, and proximal, and usually occurs ventrally in coital-related injuries.[3,12] Tears more commonly (75%) affect the right side[9] and bilateral corporal tears occur in 4–14% of patients.[7,13] Urethral injury seems to be diagnosed more commonly in the USA and Europe (20–38%) compared to Asia (0–3%) and the likelihood of a urethral injury is increased in cases of bilateral corporal tears.[11,12]

Penile fracture is largely a clinical diagnosis based on history and physical examination and the diagnosis is usually readily made based on clinical features.[11] At the time of injury, the man usually reports hearing a cracking sound. Immediate detumescence and pain usually follows.[3] Acute swelling and penile deformity may give rise to the 'eggplant' or 'aubergine' sign.[9] If Buck's fascia is intact, the underlying clot over the fracture site may be palpated as a discrete swelling over which the penile skin can be rolled giving rise to the 'rolling sign.' This sign may be elicited in the acute setting as originally described by Naraynsingh and Raju.[14] but may be particularly well illustrated in delayed presentations with resolution of the surrounding oedema.[14,15] Due to the mass effect of the haematoma, the penis may be deviated to the contralateral side.[12] Gross or microscopic haematuria, blood at the meatus, or difficulty voiding may be indicative of urethral injury, but this cannot be ruled out in their absence.[16]

In most cases the diagnosis of fractured penis can be made clinically without the need for further investigations,[17] but some studies may be necessary in equivocal cases or specific clinical scenarios. Urinalysis should be undertaken to assess for microscopic haematuria, which may be a marker of a non-apparent urethral injury, bearing in mind that it may have a positive predictive value of around 50%.[7] Ultrasonography may detect tunical defects or haematomas and has a sensitivity of around 86% but remains very operator-dependent.[18] It is however readily available and non-invasive. An ultrasonographic grading system for these injuries has been proposed by Shukla et al.[19] to assist in the planning of surgical management. The grades range from 0–4, with Grade 0 denoting a normal tunica albuginea. Grade 1 injury represents a defect in the tunica albuginea with cavernosa involvement, Grade 2 demonstrates a haematoma in the subcutaneous tissue as well as in the corpora cavernosa, and Grade 3 suggests a more severe injury with deep fascial haematoma and involvement of the corpora spongiosum. Grade 4 injury implies urethral and vascular involvement with vascular malformation.[19]

Retrograde urethrography may be conducted in cases where urethral injury is suspected but is not always readily available.[20] Cavernosography may also be used to localise the albugineal tear and may prove useful in certain clinical scenarios, for example in the case of a suspected fracture when none can be found intraoperatively.[9] It is also not without risk, as side effects include corporal fibrosis, priapism, and contrast reactions.[21,22] MRI is an accurate modality in the imaging of penile fracture which could potentially aid localisation of the tunical rupture,[23] but it is limited by cost and availability. Practically, intraoperative flexible cystoscopy may be done at the time of repair when a urethral injury is suspected and costs little by way of time and morbidity.[5]

Penile fractures have been managed conservatively in the past. Conservative measures have included pressure dressings, cold compresses, and anti-inflammatory drugs. Conservative management has lost favour because of the high rate of complications compared to immediate surgical repair, including infected haematoma, abscess, erectile dysfunction, penile curvature, and arteriovenous fistula. In addition, these patients may have prolonged hospitalisation (as long as 2 weeks).[24] In a 22-year review of 29 patients, 12 treated with immediate surgery and 17

with conservative management, Muentener et al.[25] noted a significantly higher rate of complications in the conservatively treated group. The surgically managed patients were more likely (92% versus 59%) to have a good outcome. This has led to the adoption of immediate repair as the standard of care in penile fractures.[5,9]

Most authors, as discussed, advocate early repair of penile fractures. This is not, however, the only approach, and a case may certainly be made for a late delayed repair, which should not be confused with the conservative management mentioned above. During the early period following injury, extensive soft tissue oedema makes clinical identification of the injury site difficult and full exposure would require a circumcising degloving incision. Such extensive dissection has been associated with complications such as skin necrosis and sepsis in as many as 66% of patients.[26] If presentation is delayed by several days, tissues may in fact still be friable, making repair more difficult. Naraynsingh et al.[15] note that a 7–12 day waiting period allows resolution of tissue oedema. Since most of the clot is trapped by Buck's fascia and is localised to the site of injury, the swelling resolves much less quickly at the site of the fracture. This produces a well circumscribed swelling over the fracture site over which the overlying skin may be rolled and has been termed the 'rolling sign' (Figure 1). By allowing resolution of tissue oedema the fracture may be accurately localised and repaired via a small direct incision as discussed below.[15] In a seminal prospective study, Nasser and Mostafa[27] reported on late delayed repair among 24 men presenting late (>24 hours) following penile fracture. In this series, patients underwent conservative treatment for 7–12 days following which surgical repair of their fractures was carried out under local anaesthesia. The authors reported excellent outcomes, with all patients regaining sexual function at 4–6 weeks.[27] Appropriate patient selection is key however, as the patient should have no urethral injury. One retrospective study did note an increased rate of erectile dysfunction among patients undergoing delayed repair, with Bozzini et al.[28] noting worse outcomes among men operated on after 8.23 hours compared with before 8.23 hours. However, a recent systematic review of 12 studies involving 502 patients reported no difference in erectile dysfunction or scar formation between immediate and delayed repair.[29] The authors have employed this delayed technique to good effect.

Numerous incisions have been used, among them the circumcising degloving, inguinoscrotal, midline penoscrotal, and lateral incisions.[11] The circumferential degloving incision has gained popularity among many surgeons. Ozcan et al.[30] cite the fact that in up to 38% of cases there is an adjacent urethral rupture, arguing that a degloving incision allows adequate examination of the corpus spongiosum and avoids missing a urethral injury. They also point to the benefits of good exposure in cases in which there is rupture of the dorsal vein without corporeal injury. The subcoronal approach is associated with a reduced risk of scarring as compared to longitudinal incisions.[30] The penoscrotal incision also affords excellent access to the proximal penis, which is more commonly the site of injury. This incision avoids degloving, which is sometimes challenging in a swollen penis, and may be extended as necessary. Mazaris et al.[31] described the successful application of this incision among eight patients undergoing immediate repair. The penoscrotal incision may also be used in cases of delayed repair.[32]

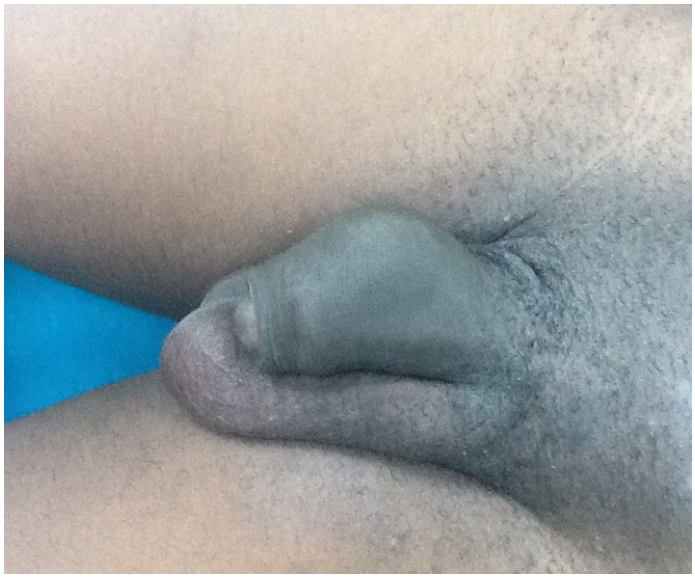

Figure 1: Delayed repair often allows localisation of the fracture site, seen here as a swelling on the shaft.

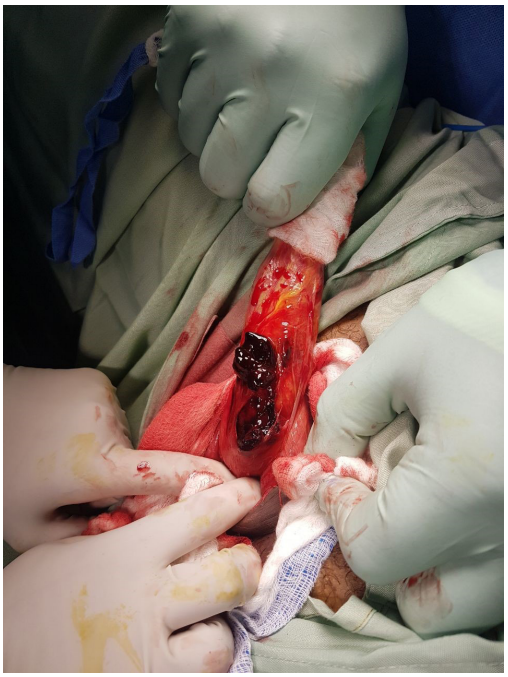

Figure 2: Degloving incision and identification of the fracture site.

Figure 3: Evacuation of clot and freshening of tunical edges prior to closure.

There are, however, other choices of incision. Naraynsingh et al.[15,33] have advocated in several publications repair via a small localised incision over the site of injury. This localised incision lends itself to a same day procedure under local anaesthesia and involves much less dissection, and by extension potentially less trauma, to neurovascular structures. The same authors have used a simple direct incision technique in both the acute and delayed repair once they were clinically able to localise the fracture site. This has subsequently been validated as safe and effective in a larger series of patients who underwent delayed repair.[27] Proponents suggest that a localised incision may avoid the potential complications of a general or regional anaesthesia as well as those associated with a degloving incision such as abscess, wound infection, or subcoronal skin necrosis.[26]

Regardless of choice of incision, the principles of repair as are follows:[9]

- Exposure
- Evacuation of the haematoma
- Identification of the site of fracture (Figure 2)
- Wound toilet and freshening of the tunical edges (Figure 3)
- Suturing of tears in the tunica albuginea
- Restoration of the urethral integrity

Naraynsingh and Raju recommend closure with running or interrupted absorbable sutures.[14] In contrast, some authors favour non-absorbable sutures, citing the fact that they hold the tunical edges together for a long time even in the face of varied intracorporeal pressure changes. However, foreign body granulomas, stitch sinus, and palpable knots may complicate the use of non-absorbable sutures. The problem of palpable knots may be circumvented by inverting the knots.[34] Practically speaking, the authors have used a range of different sutures with equally satisfactory results although our preference is for absorbable materials, such as polydiaxanone or poliglecaprone, using a running stitch.

Management of urethral injuries deserves special mention. Partial tears may be managed successfully by urethral catheterisation, closure over a urethral catheter, or suprapubic cystostomy.[9,35] While it has been traditionally advised that complete urethral ruptures be additionally diverted via a suprapubic cystostomy, Singh[36] advises that such diversion should only be offered to complex cases with wide distraction defects or when significant sepsis precludes primary urethroplasty. Corporal-urethral fistulae have been reported due to the proximity of the corporal and urethral repairs[37] and the development of a sub-Dartos flap with interposition between the corporal and urethral

repairs has been described in the literature.[11,16] For urethral repair, the authors would recommend absorbable suture material. The authors' choice of suture is poliglecaprone (Monocryl). It should be noted that non-operative management of urethral injuries has been described.[35] In cases where the patient is able to void spontaneously, and in which there is free flow of contrast past the lesion, the authors suggest observation, citing the potential for stricture formation which may follow urethral repair.

Opinion is divided on the use of a perioperative urethral catheter. Some authors recommend routine catheterisation at the time of surgery as this not only aids dissection but facilitates easy urethral repair in the event of a tear.[11,38] Others have used it when injuries were close to the urethra.[6] When there is a urethral injury and a catheter is used to scaffold the repair it should be kept in place for 7–10 days.[11] Early erections following surgery are a concern as this has been associated with dehiscence of the corporal repair.[38] A number of medications, such as antiandrogens or sedatives, have been used to suppress erections and some recent publications still advocate their use.[2] However, it has been argued that these may be unnecessary because postoperative pain is likely to prevent rigid erections and indeed this issue did not arise in any of the authors' cases.[11] While some authors have recommended as much as a 6-week period of abstinence,[21] Uygur et al.[39] reported no recurrences among 32 patients, a significant number of whom resumed intercourse at two weeks.

Surgical repair of penile fractures is advocated by the majority of investigators to diminish the incidence of fracture complications, but even this approach has its attendant sequelae. Several recent series have quoted incidence rates of postoperative complications to be around 6–25%. The most frequent complications after surgical repair of the fractured penis are painful erection and intercourse, penile deformity or deviation, skin necrosis, erectile dysfunction, and urethral strictures.[2] Zargooshi[4] reported excellent sexual function among >300 patients who underwent repair.

Occasionally, other conditions may masquerade as penile fractures and are treated as such, resulting in negative penile explorations. The most frequent mimics are dorsal arterial and venous ruptures, which are often only distinguishable from corporal injury by cavernosography.[40,41] Traumatic intercourse may also result in penile suspensory ligament rupture, with a presenting history similar to that of penile fractures, but the examination finding of a floppy penis is usually the discerning feature.[42] Among 86 patients, Moslemi[43] noted that almost all were able to attain good erections but did note a 2.3% incidence of penile curvature.

CONCLUSION

Fracture of the penis in the West usually occurs following intercourse, when the erect penis hits the perineum or symphysis pubis. While imaging may be used as an adjunct to aid diagnosis, especially in equivocal cases, it remains largely a clinical diagnosis. Immediate repair has been established as the standard of care, but delayed repair has been employed with equally successful outcomes. The degloving incision facilitates very good exposure but repair may be undertaken via a simple direct incision if the fracture site can be localised. Urethral injuries usually require repair although successful non-operative management of small partial tears has been described. Postoperative medications to suppress erections have not been of proven benefit.

References

1. Penson DF et al. The hemodynamic pathophysiology of impotence following blunt trauma to the erect penis. J Urol. 1992;148(4):1171-80.
2. Derouiche A et al. Management of penile fractures complicated by urethral rupture. Int J Impot Res. 2008;20(1):111-4.
3. Eke N. Fracture of the penis. Br J Surg. 2002;89(5):555-65.
4. Zargooshi J. Sexual function and tunica albuginea wound healing following penile fracture: An 18-year follow-up study of 352 patients from Kermanshah, Iran. J Sex Med. 2009;6(4):1141-50.
5. Mirzazadeh M et al. Penile fracture epidemiology, diagnosis and management in Iran: A narrative review. Transl Androl Urol. 2017;6(2):158-66.

6. Zargooshi J. Penile fracture in Kermanshah, Iran: The long-term results of surgical treatment. BJU Int. 2002;89(9):890-4.
7. Jack GS et al. Current treatment options for penile fractures. Rev Urol. 2004;6(3):114-20.
8. Anselm O, Okechuhwu O. Penile fracture from entrapment of an erect penis in the African Bamboo bed: A case report. African J Urol. 2010;16(1):24-6.
9. Al-Shaiji TF et al. Fractured penis: Diagnosis and management. J Sex Med. 2009;6(12):3231-40.
10. De Rose AF et al. Traumatic rupture of the corpora cavernosa: New physiopathologic acquisitions. Urology. 2001;57(2):319-22.
11. Kamdar C et al. Penile fracture: Preoperative evaluation and surgical technique for optimal patient outcome. BJU Int. 2008;102(11): 1640-4.
12. Masarani M, Dinneen M. Penile fracture: Diagnosis and management. Trends Urol Mens Health. 2007;12(5):20-4.
13. Koifman L et al. Penile fracture: Diagnosis, treatment and outcomes of 150 patients. Urology. 2010;76(6):1488-92.
14. Naraynsingh V, Raju GC. Fracture of the penis. Br J Surg. 1985;72(4):305-6.
15. Naraynsingh V et al. Late delayed repair of fractured penis. J Androl. 2010;31(2):231-3.
16. Amit A et al. Penile fracture and associated urethral injury: Experience at a tertiary care hospital. J Can Urol Assoc. 2013;7(3-4):E168-70.
17. Amer T et al. Penile fracture: A meta-analysis. Urol Int. 2016;96(3):315-29.
18. Koga S et al. Sonography in fracture of the penis. Br J Urol. 1993;72(2):228-9.
19. Shukla AK et al. Role of ultraosonography in grading of penile fractures. J Clin Diagn Res. 2015;9(4):TC01-3.
20. Agrawal SK et al. Experience with penile fractures in Saudi Arabia. Br J Urol. 1991;67(6):644-6.
21. Sawh SL et al. Fractured penis: A review. Int J Impot Res. 2008;20(4):366-9.
22. Pliskow RJ, Ohme RK. Corpus cavernosography in acute "fracture" of the penis. AJR Am J Roentgenol. 1979;133(2):331-2.
23. Abolyosr A et al. The management of penile fracture based on clinical and magnetic resonance imaging findings. BJU Int. 2005;96(3):373-7.
24. Nicolaisen GS et al. Rupture of the corpus cavernosum: Surgical management. J Urol. 1983;130(5):917-9.
25. Muentener M et al. Long-term experience with surgical and conservative treatment of penile fracture. J Urol. 2004;172(2):576-9.
26. Mansi MK et al. Experience with penile fractures in Egypt: Long-term results of immediate surgical repair. J Trauma. 1993;35(1):67-70.
27. Nasser TA, Mostafa T. Delayed surgical repair of penile fracture under local anesthesia. J Sex Med. 2008;5(10):2464-9.
28. Bozzini G et al. Delaying surgical treatment of penile fracture results in poor functional outcomes: Results from a large retrospective multicenter European study. Eur Urol Focus. 2018;4(1):106-10.
29. Wong NC et al. Can it wait? A systematic review of immediate vs. delayed surgical repair of penile fractures. J Can Urol Assoc J. 2017;11(1-2):53-60.
30. Ozcan KP et al. Response to the letter to the editor entitled 'Fluorodeoxyglucose positron emission tomography/computed tomography standardised uptake value in discriminating benign versus malignant adrenal lesions: An open and debated issue'. Nucl Med Commun. 2011;32(6):543-4.
31. Mazaris EM et al. Penile fractures: Immediate surgical approach with a midline ventral incision. BJU Int. 2009;104(4):520-3.
32. Fariña-Pérez LA. Delayed consultation and treatment of penile fracture: A case report. Available at: https://www.scribd.com/document/363229608/Delayed-Consultation-and-Treatment-of-Penile-Fracture. Last accessed: 13 March 2019.
33. Naraynsingh V et al. Simple repair of fractured penis. J R Coll Surg Edinb. 1998;43(2):97-8.
34. Prasanna GV et al. Refracture penis. Case Rep Clin Pract Rev. 2003;4(2):217-8.
35. Maharaj D, Naraynsingh V. Fracture of the penis with urethral rupture. Injury. 1998;29(6):48.
36. Singh I et al. Bilateral corporal fracture with urethral rupture following intercourse - Case report with review of the literature. J Clin Diagn Res. 2008;21017-9.
37. Hargreaves DG, Plail RO. Fracture of the penis causing a corporo-urethral fistula. Br J Urol. 1994;73(1):97.
38. Mydlo JH. Surgeon experience with penile fracture. J Urol. 2001;166(2):526-8.
39. Uygur MC et al. 13 years' experience of penile fracture. Scand J Urol Nephrol. 1997;31(3):265-6.
40. Armenakas NA et al. Traumatic avulsion of the dorsal penile artery mimicking a penile fracture. J Urol. 2001;166(2):619.
41. Baran C et al. Superficial dorsal vein rupture imitating penile fracture. Korean J Urol. 2011;52(4):293-4.
42. Kropman RC et al. Traumatic rupture of the suspensory ligament of the penis. Case report. Scand J Urol Nephrol. 1993;27(1):123-4.
43. Moslemi MK. Evaluation of epidemiology, concomitant urethral disruption and seasonal variation of penile fracture: A report of 86 cases. J Can Urol Assoc. 2013;7(9-10): E572-5.

Repair of Distal Hypospadias: Cosmetic or Reconstructive?

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Abstract

Objective: Hypospadias is one of the most common congenital anomalies of male genitalia and is usually repaired in the first 2 years of life. Regarding distal forms of hypospadias, however, controversies surrounding the need for surgical repair may lead to delayed referral secondary to symptoms. This article reviews the authors' experience in boys who presented with symptoms secondary to an untreated distal hypospadias.

Materials and methods: The authors reviewed their prospectively maintained database and included all children who were secondarily referred because of symptoms due to untreated distal hypospadias in the last 5 years. The data were reviewed and analysed.

Results: Seventeen patients were identified. The median age at referral was 118 months. Symptoms at presentation included poor stream, straining during voiding, incontinence, and unhappiness related to cosmesis. Surgical correction included meatoplasty or tubularised incised plate urethroplasty. The choice between foreskin reconstruction or circumcision was based on parental preference.

Conclusion: The authors have presented a cohort of children with untreated distal hypospadias associated with functional and cosmetic problems. Both could be underestimated at birth, leading to problems in late childhood. Viewing repair of distal hypospadias as a purely cosmetic surgery is to disregard the nature of the anomaly and its associated implications.

INTRODUCTION

Hypospadias is one of the most common congenital abnormalities of male external genitalia with an incidence of 1 in 200–300 live male births, and its correction represents a common surgical procedure performed by paediatric urologists.[1,2] Based on the severity and the location of the meatus, hypospadias is classically divided into proximal, mid-shaft, and distal forms, with the latter accounting for 70–80% of cases.[3] Indications for undergoing a surgical repair are mainly related to function and cosmesis.

Distal forms are often labelled as 'functionally normal' and therefore their repair is debated.[4] While, in general, babies born with hypospadias are referred to specialist services and operated on within the first 2 years of life, parents of children with distal hypospadias are sometimes

reassured that no functional impairment is associated with this defect. As a result of this reassurance, no referral is made, leaving the child with an untreated hypospadias. The symptoms of untreated hypospadias primarily include a downward deflected urine stream, dysuria, and urinary incontinence.

The authors aimed to review the children referred to their department with hypospadias, focussing on late referral of children with untreated distal hypospadias.

MATERIALS AND METHODS

The authors reviewed their prospectively maintained database for all hypospadias patients referred to their unit. They collected data for all patients with distal hypospadias referred over the last 5 years (from January 2014–December 2018), including all children who were secondarily referred with symptoms related to an untreated distal hypospadias. The authors considered all children who presented to them with symptoms related to their hypospadias after 3 years of age. These patients were previously seen by other healthcare professionals (paediatricians and group practice); the authors defined this as late referral. Patients who had a previous hypospadias repair and presented at a later age with complications were not included.

The patients' referral letters, medical notes, assessments, and operation documents were reviewed. Symptoms at presentation, clinical findings, and the procedures performed were recorded and evaluated.

RESULTS

In the analysed period, the authors identified 17 patients who presented with symptoms secondary to an untreated distal hypospadias. Patient characteristics are set out in Table 1.

Table 1: Patient characteristics.

Serial number	Age at presentation (months)	Symptoms/Complaints/Relevant conditions	Operative findings	Procedures performed
1	142	Unhappy with cosmesis	Glanular stenotic meatus	Meatoplasty and foreskin reconstruction
2	120	Day time wetting Poor stream	Glanular stenotic meatus	Meatal advancement and modified circumcision
3	120	Poor stream Stranguria	Subcoronal	TIP
4	119	Poor stream Balanitis	Coronal stenotic meatus	Meatoplasty and foreskin reconstruction
5	117	Unable to void straight	Subcoronal	TIP
6	113	Spraying Incomplete voiding Stranguria	Glanular stenotic meatus	Meatoplasty and modified circumcision
7	105	Struggling to pass urine	Glanular pinhole meatus	TIP and foreskin reconstruction
8	89	Unhappy with cosmesis	Glanular stenotic meatus	Meatoplasty and foreskin reconstruction
9	59	Day time wetting	Subcoronal pinhole meatus	TIP and foreskin reconstruction

Table 1 continued.

Serial number	Age at presentation (months)	Symptoms/Complaints/Relevant conditions	Operative findings	Procedures performed
10	51	Urine stream deflects downwards	Subcoronal pinhole meatus	TIP
11	64	Poor stream Stranguria Abdominal straining during voiding	Glanular meatal stenosis	Meatoplasty and modified circumcision
12	106	Stranguria Urinary incontinence Autism	Coronal pinhole meatus	TIP and foreskin reconstruction
13	120	Unhappy with cosmesis	Glanular pinhole meatus	Meatoplasty and foreskin reconstruction
14	149	Poor stream	Coronal pinhole meatus	TIP
15	40	Urine stream deflected downwards Spraying	Glanular pinhole meatus	TIP
16	40	Urine stream deflected downwards Balanitis	Glanular pinhole meatus	Meatoplasty and modified circumcision
17	48	Urine stream deflected downwards	Coronal pinhole meatus	Awaiting surgery

TIP: tubularised incised plate urethroplasty.

The median age at referral was 118 months (range: 40–149 months). Three boys (Patients 1, 8, and 13) were asymptomatic but unhappy with the cosmesis. The remaining children (n=14) presented with symptoms. Common symptoms reported were poor stream, straining during voiding, and daytime wetting.

In nine boys, the meatus was glanular and, in the remainder, the meatus was either coronal or subcoronal. All patients with glanular hypospadias who were found to have meatal stenosis were offered a meatoplasty. Patients with coronal and subcoronal hypospadias underwent a tubularised incised plate urethroplasty. Depending on parental preference, the foreskin was either preserved and reconstructed (n=7) or removed (n=9) (Patient 17 is currently awaiting surgery). Most children presented with a stenotic meatus (Figure 1) and a narrow stream (Figure 2A). In these children, a preoperative uroflow study showed a plateau curve suggesting an obstructed flow (Figure 3). The authors did not conduct any ultrasonography in any patients. Some of the children who presented with daytime (and night-time) wetting reported having previously failed the classic management strategies for treating urinary incontinence.[5]

In particular, as an example, before being referred to the authors' unit, Patient 2 underwent many assessments and medical treatments (including being referred to a psychologist) to correct what was considered to be primary urinary incontinence. His symptoms completely resolved following the operation. In another boy (Patient 12), who was still in nappies at the age of 8 years, the incontinence was considered secondary to mild autistic condition, thus the parents were told that no solution was available, and potty training was not possible.

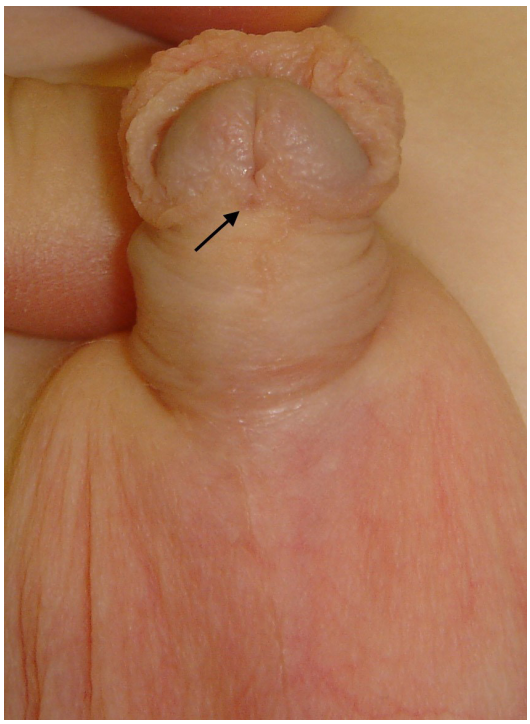


Figure 1: Preoperative image of an untreated hypospadias.

The arrow points to the pin-hole coronal meatus.

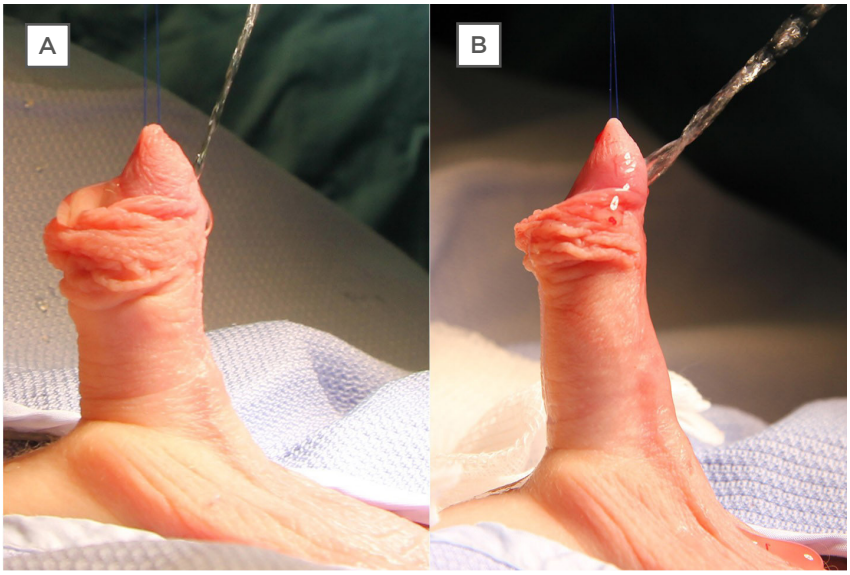


Figure 2: A) Shows the stream assessed intra-operatively before meatoplasty and B) after meatoplasty.

DISCUSSION

Repair of distal hypospadias, despite being a commonly performed procedure by paediatric urologists, is still a controversial matter. Many aspects of the treatment are debated, such as the fate of the foreskin,[6] the need for postoperative stenting[7] or for antibiotic prophylaxis,[8] and, ultimately, whether it should be considered as a functional or cosmetic repair.[4,9]

In a recent editorial, Snodgrass and Bush[9] argued that distal hypospadias repair should not be

considered a cosmetic operation. The authors agree with this and believe that the presented series could represent further supporting evidence for that position.

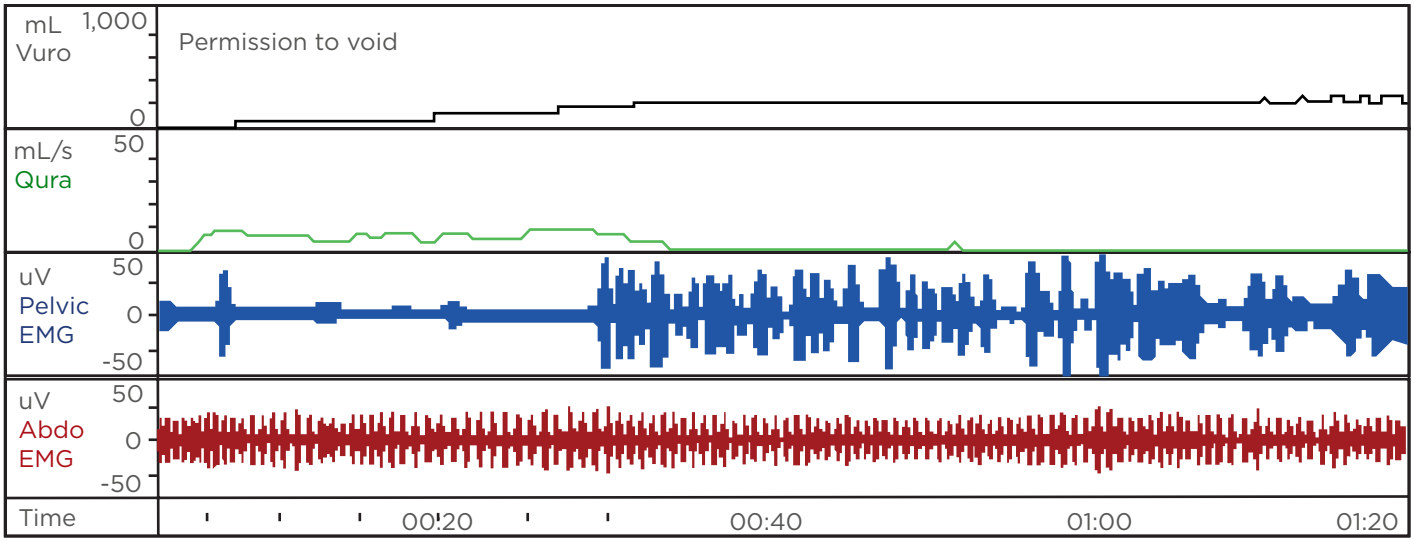
A penis affected by hypospadias is not developed normally and if the condition is left untreated, it can be associated with multiple symptoms.[9] The symptoms are primarily due to the presence of an abnormal meatus and include voiding with a downward deflected urine stream, dysuria, strangury, and urinary incontinence.[10,11]

Similar to some of the authors' patients, in a series published in 2009, an obstructive urinary flow pattern was observed preoperatively in 25% (16 out of 63) of patients with hypospadias who were aged 5–11 years. In one-third of them, the presence of meatal stenosis was then confirmed intraoperatively.[12]

Similar observations were also reported by Oslen et al.,[13] who found low maximum flow rates with plateau shaped curves in 31% of infants with hypospadias. Presence of a meatal narrowing is a reported cause of urinary symptoms, as identified in some of the authors' patients. If it goes undetected or underestimated, it could lead to unnecessary treatments and major distress.[14,15]

Cases like the two children mentioned above, where their incontinence was considered primary or related to autism, should never occur and could have simply been avoided by a thorough physical examination and an appropriate early referral to a paediatric urologist.

Graph



Uroflow results

VOID	7/180/198
Qmax	6.6 mL/s
Time to Qmax	2 s
Voided volume	181 mL
Flow time	58 s
Voiding time	64 s
Average flow rate	3.1 mL/s
Residual urine	198 mL

Figure 3: Shows uroflow in patient with meatal stenosis. The Qmax is 6.6 mL/s with a plateau shaped curve suggesting obstructed flow.

EMG: electromyography; Qmax: maximum flow rate.

Only a few reports are available about patients with uncorrected hypospadias. Fichtner et al.,[4] in a study conducted in 500 men, found a 13% incidence of distal hypospadias (glanular, coronal, and subcoronal). Of these, 63% reported being unaware of any penile abnormality and that they had a normal sexual history. The authors also pointed out that these patients were able to void in standing position with a straight and single stream, concluding that the repair of distal hypospadias should be considered a cosmetic surgery. Similarly, in a report by Dodds et al.,[16] in a cohort of 56 adults with hypospadias (9 of those with previous failed surgical repair and 47 untreated), it was suggested that many of them appeared to have adapted to their congenital anomaly without any surgical correction.

However, a different message is provided in a survey reported by Schlomer et al.[17] They recruited 736 adult men who completed an online questionnaire regarding penile self-anatomy; of these men, 52 (7.1%) self-identified as having a possible untreated hypospadias. Among all responders, men with a possible untreated hypospadias reported adverse outcomes compared to normal men. The most significant adverse outcomes appeared to be the presence of penile curvature and difficulty with intercourse caused by the penile curvature.

Furthermore, as reported by Snodgrass and Bush in their editorial,[9] a survey performed by Keays et al.[10] showed that 37% of uncorrected hypospadias patients had a deviated stream and only 39% could void straight. In addition, 54% were dissatisfied with their voiding, with 29% being very dissatisfied. This survey also covered patients' satisfaction regarding cosmesis and reported that 33% of men with uncorrected hypospadias were dissatisfied with penile appearance, 41% were worried about "what others would think about it," and 46% reported being teased because of it.[10] In the current series, despite the absence of functional problems, 3 boys expressed their dissatisfaction regarding the cosmesis and requested a surgical intervention.

A possible argument against early correction of distal hypospadias could be the perception that delaying the decision would save parents from having to be responsible for making a decision on their son's behalf and could reduce the risk of parental regret.[18,19] Although this view is understandable and could be considered, it should not be implemented if the consequence carries the risk of years of suffering and embarrassment.[10] A study from Nigeria[20] quoted two peaks of age at surgery. One peak was noted in the age group of 1–3 years and the second peak at 5–10 years. They noted that chordee was the most common problem associated with hypospadias. The authors cited problems with paediatric anaesthesia resulting in the later age group for surgical correction.

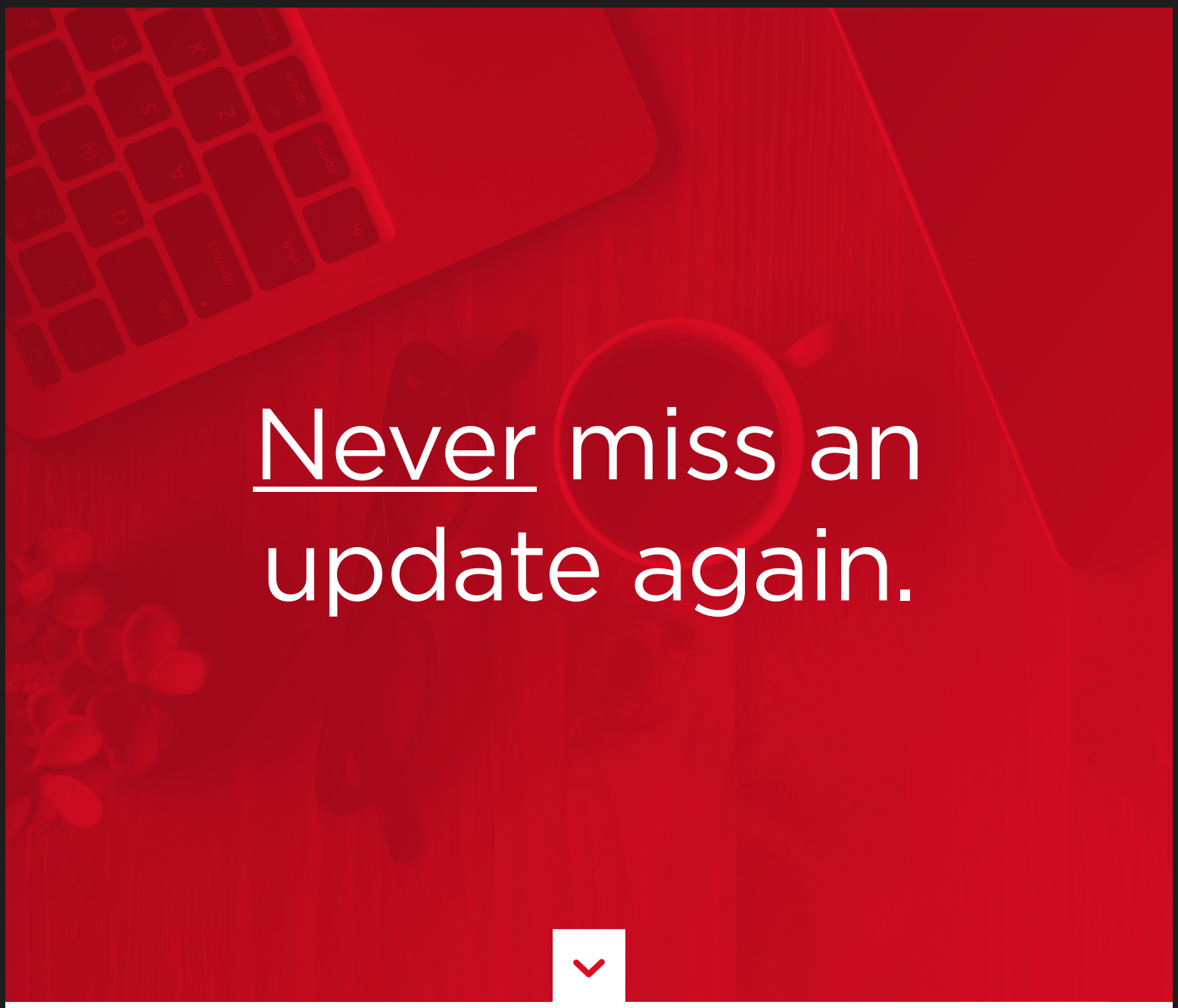
Surgical correction of distal hypospadias carries minor risks, but outcomes in the majority of cases are successful and, despite some variations among different techniques, complication rates are relatively low.[21-23] In view of the presented case series, the authors believe that correction of distal hypospadias is not a cosmetic surgery and would recommend that all children with hypospadias, regardless of the severity, should be referred to a specialist paediatric urologist. This will provide the child with the best possible assessment to identify those at risk of developing functional issues (those with a pinhole/stenotic meatus) and will give parents the option to be appropriately counselled regarding the risks and benefits of surgical and conservative management.

CONCLUSION

Distal hypospadias can be associated with both functional and cosmetic problems that may be underestimated at birth and generate symptoms at an older age. Repair can be safely achieved with minimal risk of complications and can easily be performed in infancy, thereby avoiding problems which can develop later in life. To consider the repair of distal hypospadias as a purely cosmetic surgery is to disregard the nature of the anomaly and its associated implications.

References

1. Nelson CP et al. The increasing incidence of congenital penile anomalies in the United States. J Urol. 2005;174(4 Pt 2):1573-6.
2. Schnack TH et al. Familial coaggregation of cryptorchidism and hypospadias. Epidemiology. 2010;21(1):109-13.
3. Duckett JW, "Hypospadias," Walsh C et al. (eds), Campbell's Urology (1998) 7th edition, vol 2, Philadelphia: WB Saunders, pp. 2094-6.
4. Fichtner J et al. Analysis of meatal location in 500 men: Wide variation questions need to meatal advancement in all pediatric anterior hypospadias cases. J Urol. 1995;154(2 Pt 2):833-4.
5. Chang SJ et al. Treatment of daytime urinary incontinence: A standardization document from the International Children's Continence Society. Neurourol Urodyn. 2017;36(1):43-50.
6. Manuele R et al. Foreskin reconstruction at the time of single-stage hypospadias repair: Is it a safe procedure? Int Urol Nephrol. 2019;51(2)187-91.
7. Chua M et al. Non-stented versus stented urethroplasty for distal hypospadias repair: A systematic review and meta-analysis. J Pediatr Urol. 2018;14(3):212-9.
8. Chua ME et al. The use of postoperative prophylactic antibiotics in stented distal hypospadias repair: A systematic review and meta-analysis. J Pediatr Urol. 2018;S1477-5131(18):30422-4.
9. Snodgrass W, Bush N. Is distal hypospadias repair mostly a cosmetic operation? J Pediatr Urol. 2018;14(4):339-40.
10. Keays MA et al. Patient reported outcomes in preoperative and postoperative patients with hypospadias. J Urol. 2016;195(4 Pt 2):1215-20.
11. Keays MA, Dave S. Current hypospadias management: Diagnosis, surgical management, and long-term patient-centred outcomes. Can Urol Assoc J. 2017;11(1-2Suppl1):S48-53.
12. Tuygun C et al. Uroflow findings in older boys with tubularized incised-plate urethroplasty. Urol Int. 2009;82(1):71-6.
13. Olsen LH et al. Urinary flow patterns in infants with distal hypospadias. J Pediatr Urol. 2011;7(4):428-32.
14. Saeedi P et al. Evaluation of the effect of meatal stenosis on the urinary tract by using ultrasonography. Urol J. 2017;14(3):3071-4.
15. Varda BK et al. Minor procedure, major impact: Patient-reported outcomes following urethral meatotomy. J Pediatr Urol. 2018;14(2):165.e1-5.
16. Dodds PR et al. Adaptation of adults to uncorrected hypospadias. Urology. 2008;71(4):682-5.
17. Schlomer B et al. Do adult men with untreated hypospadias have adverse outcomes? A pilot study using a social media advertised survey. J Pediatr Urol. 2014;10(4):672-9.
18. Lorenzo AJ et al. Decisional regret after distal hypospadias repair: Single institution prospective analysis of factors associated with subsequent parental remorse or distress. J Urol. 2014;191(5 Suppl):1558-63.
19. Ghidini F et al. Parental decisional regret after primary distal hypospadias repair: Family and surgery variables, and repair outcomes. J Urol. 2016;195(3):720-4.
20. Aisuodionoe-Shadrach OI et al. Hypospadias repair and outcome in Abuja, Nigeria: A 5-year single-centre experience. Afr J Paediatr Surg. 2015;12(1):41-4.
21. Snodgrass W. Tubularized, incised plate urethroplasty for distal hypospadias. J Urol. 1994;151(2):464-5.
22. Wilkinson DJ et al. Outcomes in distal hypospadias: A systematic review of the Mathieu and tubularized incised plate repairs. J Pediatr Urol. 2012;8(3):307-12.
23. Diamond DA et al. Advances in paediatric urology. Lancet. 2017;390(10099):1061-71.



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