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EMJ Urology

EAU Congress 2022

Editor's Pick

Primary Penile Squamous Cell Carcinoma in a Patient with Metastatic Adenocarcinoma of Colon to Liver: A Case Report

Interview

Prasanna Sooriakumaran shares insights into his current research interests and the progression of innovations in the field

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Aims and Scope

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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.

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Front cover and contents photograph: Amsterdam, Netherlands, home of the **EAU 2022**

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

It is a great pleasure to welcome you to the 2022 issue of *EMJ Urology*. This year, the 37th Annual European Association of Urology (EAU) Congress took place in Amsterdam, the Netherlands, and we have the pleasure of brining you key updates from this event.

In our clinically relevant congress feature, you will have the opportunity to read about urinary stone disease, including state-of-the-art imaging and radiation protection in endourological surgery, temporary versus lifelong medical prophylaxis in high-risk patients, and updated urolithiasis guidelines. We are delighted to also feature a round-up of EAU22 written by Christopher Chapple, EAU Secretary General, and Arnulf Stenzl, EAU Secretary General Adjunct.

In addition to the congress coverage, this journal contains fascinating reviews, research articles, and case reports. Our Editor's Pick is a case report that describes penile squamous cell carcinoma occurring simultaneously with colorectal adenocarcinoma from the colon to the liver. This has clear novelty because the patient presented with two separate tumours that were genetically unrelated. Since this article highlights a rare and educational case, it is a valuable addition to the literature. This issue also features an insightful case series showcasing the validity of minimally invasive robotic surgery for the management of locally advanced renal cell carcinoma.

I hope you enjoy reading this issue and, as always, I would like to extend our thanks to our authors, peer reviewers, and Editorial Board for the high quality of these research updates. We look forward to seeing everyone at next year's EAU Congress.

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Foreword

Dear Colleagues and Friends,

It is a great pleasure for me to introduce you to the new issue of *EMJ Urology*. In this issue, we again have a variety of very interesting papers. 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, where the latest developments of every urology subspeciality are presented and discussed. In this issue, you will have the chance to read some information that was shared at the EAU Congress held in Amsterdam, the Netherlands, and also virtually.

My selected article for the Editor's Pick in this issue is 'Primary Penile Squamous Cell Carcinoma in a Patient with Metastatic Adenocarcinoma of Colon to Liver: A Case Report' by Son et al. Penile cancer is a rare type of malignancy presenting in 1% of males, and is linked with *human papillomavirus* and immunosuppression, and if it is not detected early could spread to other regions of the body. This article outlines a case of concurrent primary penile squamous cell carcinoma with a recurrence of colorectal adenocarcinoma. The case report has a clear novelty as it presents two separate tumours that are unrelated genetically, and will be of great value to readers.

This is just one of the interesting papers in this issue of *EMJ Urology*. Additionally, you will find an infographic on bladder cancer, which covers the different types of bladder cancer, risk factors, treatment options, and so much more.

I would like to thank all the authors who contributed to this journal, as well as the Editorial Board members and reviewers. Finally, 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!

A. Erdem Canda

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EAU 2022

Review of the 37th Annual Meeting of the European Association of Urology (EAU) 2022

Location: Amsterdam, The Netherlands
Date: 1st–4th July 2022
Citation: EMJ Urol. 2022;10[1]:8-16. DOI/10.33590/emjurol/10166330. https://doi.org/10.33590/emjurol/10166330.

THE 37th Annual Meeting of the European Association of Urology (EAU) took place in Amsterdam, the Netherlands, and online between the 1st–4th July 2022. The opening ceremony began with a piano performance from the talented Wibi Soerjadi and a unique artistic display from a sand magician, who demonstrated his art by using sand alone. Christopher Chapple, EAU Secretary General, welcomed all the attendees to the first in-person Annual Congress since EAU19, which had taken place in Barcelona, Spain.

At this year's congress, there were over 2,580 presentations from 900 speakers, 56 courses, and training courses provided by the European School of Urology (ESU). Furthermore, this year held the first in-person 'Patient Day', following the success of last year, which is a special programme organised by the recently formed EAU Patient Office. The 4-day scientific programme comprised of live surgery, state-of-the-art lectures, case discussions, and dynamic debates from experts in this field. The congress had over 8,200 attendees from 124 countries, both in-person and virtually.

Chapple presented awards for the new honorary members: John Denstedt, Western University, London, Canada; Rien Nijman, University Hospital Groningen, the Netherlands; and Manfred Wirth, Technical University Dresden, Germany. The EAU Willy Gregoir Medal, which is for a significant contribution to the development of the urological specialty in Europe, was awarded to Karl-Eric Andersson, Lund University, Sweden. The Frans Debruyne Life Time Achievement Award, for a longstanding and crucial contribution to the activities and development of the EAU, was awarded to Joan Palou, University of Barcelona, Spain. The Crystal Matula Award, which is given to a young promising European urologist, was awarded to Veeru Kasivisvanathan, University College London (UCL) Hospitals NHS Foundation Trust, London, UK. For the best European paper published on minimally invasive surgery in urology, Alberto Martini, University Vita-Salute San Raffaele Scientific Institute (UniSR), Milan, Italy, received the Hans Marberger Award. For inventions and clinical contributions that have had a major influence in the treatment and/or diagnosis of a urological disease, Yvet Fradet, Laval University, Quebec, Canada, received the EAU Innovators in Urology Award. Alain Jardin, Paris, France, on behalf of Cercle Félix Guyon, was awarded the Ernest Desnos Prize, for exceptional contributions to the history of urology. The Prostate Cancer Research Award was awarded to Tobias Nordström, Karolinska Institutet, Stockholm, Sweden.

"He further covered the ways in which the field of urology has evolved over the past 50 years, and highlighted the most important developments."

"It is the 50th year of the EAU [...] it has been around for half a century," stated Chapple. Philip Van Kerrebroeck, Chairman of the EAU history office, walked the attendees through the history of the EAU. "This is the beginning of a great party [...]it will be a party that will take one year." Founded in 1972–1973, the EAU began the 50th anniversary celebration in Amsterdam, the Netherlands, where it was founded, and will conclude in Milan, Italy, at the EAU23 Congress. Firstly, Van Kerrebroeck acknowledged all of the previous secretary generals, and paid tribute to them. He further covered the ways in which the field of urology has evolved over the past 50 years, and highlighted the most important developments that took place over that period of time, and their links to European history.

Frans Debruyne, a former Secretary General, was praised for his work in the EAU for encouraging the organisers of Congress to enhance the event so that it was not only available for Europeans, but also international urologists. The EAU has reaped the fruits of his hard work as now the congress is an international event, with participants from over 124 countries, and joint sessions with urological associations worldwide including the USA, Asia, and Africa. In appreciation of Debruyne, both Chapple and Van Kerrebroeck unveiled a bust of Debruyne, which was an acknowledgment of the role he played in society at large. In his acceptance speech, he encouraged the attendees to "continue to work and let the EAU grow, not only in quantity but also, similar to what we have done the past 50 years, in quality." Debruyne praised the EAU for its tremendous efforts in improving the quality of the field of urology in Europe and also globally.

To conclude, Chapple took the opportunity to thank all the members of the EAU who planned the scientific programme, the presenters who shared their expertise and latest research, and the attendees who were joined both in-person and virtually. An overview of groundbreaking EAU press releases can also be found within this issue of *EMJ Urology*, including how gut microbes may differ in males with prostate cancer, artificial intelligence in the field of urology, and much more. With this in mind, we look forward to joining the EAU at next year's congress in Milan, Italy, where the society will conclude their 50-year anniversary celebrations. Read on for our key scientific insights from EAU's 37th Annual Meeting.

Differences in the Gut Microbiome in Males with Prostate Cancer

SIGNIFICANT differences have been observed in the gut microbiota of males with prostate cancer compared with individuals who have benign biopsies. Although this finding is an association, it might partly explain the relationship between lifestyle effects and geographical variations in prostate cancer. The study was presented at this year's EAU22, which took place between 1st–4th July in Amsterdam, the Netherlands.

Gut microbiota dysbiosis has been implicated in a range of conditions, including in organs that are far from the intestines; however, the connection between the gut microbiome and prostate cancer remains to be elucidated. For this reason, Peter Boström and collaborators from the University of Turku, Finland, collected samples from patients enrolled in a prospective multicentre clinical trial. The research team sequenced the gut microbiota from 181 males with suspected prostate cancer who where undergoing prostate cancer diagnostics. Samples were collected at the time of their biopsies after MRI scans.

In total, 60% of the males were diagnosed with prostate cancer. Their gut microbiota profiles were characterised by increased levels of members of the family *Erysipelotrichaceae* and *Shigella*, as well as lower levels of *Jonquetella*, *Moryella*, *Anaeroglobus*, and *Corynebacterium*.

Boström commented on the relevance of the results and highlighted directions for future research: "There are significant variations in prostate cancer rates around the world, which could be due to genetic factors or differences in healthcare policies, but also variance in lifestyle and diet. The difference in gut microbiota between men with and without prostate cancer could underpin some of these variations. More research is needed to look at the potential for using gut microbiota for both diagnostic and preventive strategies."

> **"The connection between the gut microbiome and prostate cancer remains to be elucidated."**

Lars Dyrskjøt Andersen, Professor of Molecular Medicine at Aarhus University, Denmark, and member of the EAU22 Scientific Congress Committee of Urology, also emphasised that this was a notable finding from a large and well-conducted study. Although no cause-and-effect measures could be determined based on this, Andersen pointed out that the gut microbiota was an important area to investigate in order to further understand prostate cancer risk.

New Study Supports Prostate Cancer Screening Programme

NEW evidence supports the introduction of a targeted risk-based screening programme for prostate cancer. The study, classified as the world's largest prostate cancer screening study, was presented at the annual EAU22 Congress, which took place on 1st–4th July, and found that those who undergo screening see their disease progress slower following diagnosis, spending more time in the earlier stages with no signs of disease progression.

The researchers, from the Erasmus MC Cancer Institute, University Medical Centre, Rotterdam, the Netherlands, examined data from over 43,000 males in the Dutch cohort from the 2009 European Randomised Study of Screening for Prostate Cancer (ERSPC), to determine the length of time it took for the disease to progress from one stage to the next after diagnosis. The stages were defined as biochemical recurrence, when the cancer had returned following treatment with radiotherapy or surgery, and the metastatic disease stage, when the cancer had spread to other organs of the body.

This novel analysis showed that when the disease had been found through a screening programme, the patients remained a year longer without their cancer progressing on to the next stage, compared to men in whom the cancer had been detected through normal clinical practice. However, the data showed that, once the cancer entered the metastatic disease phase, the length of time men spent in that stage were similar for both groups.

> **"The results further support the need for a risk-based screening programme to help reduce prostate cancer mortality rates."**

The results further support the need for a risk-based screening programme to help reduce prostate cancer mortality rates. Hendrik Van Poppel, Adjunct Secretary General of the EAU, stated: "The systematic and personalised approach to screening advocated by the EAU will significantly reduce the likelihood of over-diagnosing or over-treating cancers that pose minimal threat. But, most importantly, it will preserve the best possible quality of life for prostate cancer patients, and it will save lives." ●

Machine Learning Beneficial for Urology Patients

AN ARTIFICIAL intelligence (AI) algorithm has been trained to identify abnormal urine flows. It is hoped that this deep-learning tool could be used to effectively monitor urology patients at home.

In information presented at EAU22, Amsterdam, the Netherlands, studies found that the Audioflow deep-learning tool was almost as effective as specialist machines currently used in clinics. Researchers also discovered that similar results are achieved in assessing the flow of urine, compared with urology residents, achieving a rate of agreement of 84%. The study was based on the detection of sound created by urine when in a soundproof environment.

Currently, patients with symptoms have to urinate into a funnel during their outpatient hospital visits; this funnel is connected to a uroflowmeter, which records information about the patient's flow. As access to hospital care has been limited during the COVID-19 pandemic, and patients have been unable to access usual services in some cases, this test can be time-consuming to wait for in healthcare settings due to demand.

The algorithm, created by colleagues at the Singapore General Hospital, Singapore, was tested with a cohort of 534 male participants between December 2017 and July 2019. All participants were asked to use a uroflowmetry machine positioned in a soundproof room, and also to record their urination on a smartphone. With 220 recordings, the AI was able to learn to estimate flow rate, volume, and time taken. However, it does not yet have the ability to differentiate between the different urinary flows of males and females, as the study was carried out using male participants only.

The overall aim of the study was to create an app for patients, who will then have the ability to monitor themselves at home. Audioflow will be rolled out via primary care physicians, so that it can be tested in real-world settings. This is a promising step forward for many patients with lower urinary tract symptoms which are related to both the urethra and bladder.

Lee Han Jie, Singapore General Hospital, who led the study, commented: "Our AI can outperform some non-experts and comes close to senior consultants [...] But the real benefit is having the equivalent of a consultant in the bathroom with you, every time you go."

"As an estimated 60% of males and 57% of females are affected by lower urinary tract symptoms, the introduction of AI in healthcare settings has the ability to ameliorate treatment for many urology patients."

As an estimated 60% of males and 57% of females are affected by lower urinary tract symptoms, the introduction of AI in healthcare settings has the ability to ameliorate treatment for many urology patients.

Applications of Artifical Intelligence Datasets for Prostate Cancer Diagnosis and Prognosis

THE LARGEST dataset of prostate cancer biopsies has been created by researchers in Sweden, who, at the EAU22 from the 1st–4th July 2022, called for increased co-ordination and focus on large scale clinical trials using artificial intelligence (AI) to enhance diagnosis, prognostication, and treatment selection. The database, containing over 95,000 images, has been created to allow the training of AI systems in diagnosis and grading of prostate cancer to aid the shortage of both generalist and specialist uropathologists.

"Grading prostate cancer is a key step in deciding on appropriate treatment, but it's a fairly subjective process and differences between pathologists' assessments can sometimes be large," stated Kimmo Kartsalo, Postdoctoral Researcher at the Karolinska Institutet (KI), Stockholm, Sweden, presenting at the EAU2022.

A collaboration of researchers from the KI; Radbound University Medical Centre (UMC), Nijmegen, the Netherlands; University of Turku, Finland; and Google Health, Menlo Park, California, USA, identified that due to the wide-ranging variety in the methodology different clinics use to prepare slides from diverse patient populations, many of the available algorithms did not have the capacity for universal application. The novel algorithm was created and trained on over 10,000 biopsy images, with top performing algorithms outperforming general pathologists and on average matching the specificity of specialist uropathologists.

Biopsies from a clinical trial in Sweden that lasted over 4 years were used to prepare the data set of 95,000 images. The extended dataset was intended to ensure that the algorithm can account for the additional complexity that is found in clinical settings such as rare disease and benign situations that mimic cancer.

> **"AI holds great promise and can benefit patients everywhere but in order to achieve this promise, we need an international effort to collect datasets that are representative of the variation in technical approaches and between patients."**

"AI holds great promise and can benefit patients everywhere but in order to achieve this promise, we need an international effort to collect datasets that are representative of the variation in technical approaches and between patients. The combination of our vast database and our colleagues' algorithms is beginning to show how we can really work together to make a big difference for clinicians and patients," stated Nita Mulliqi from the KI.

Mulliqi further identified four areas that are key to ensuring improving grading and prognosis of prostate cancer using AI. These include, scanner calibration, improved algorithms, upscaling datasets, and modelling for morphological heterogeneity. The researchers emphasised the value that AI could provide in the future, stating that so far AI has only been used to replicate grading carried out by uropathologists; however, in the future it has the potential to identify elements in images and predict clinical outcomes directly.

New Study Demonstrates that MRI Is Still the Gold-Standard for Prostate Cancer Imaging

IN NOVEL findings presented at EAU22 in Amsterdam, the Netherlands, researchers highlighted how MRI scans can be used to detect prostate cancer with a significantly higher degree of accuracy than the newer, prostate specific membrane antigen (PSMA) PET/CT scanning technique. This technique uses a radioactive dye to identify prostate cancer cells through identifying PSMA, which is found on the cell surface and can be used to measure both progression and recurrence of disease.

The PEDAL trial recruited participants identified as at risk of prostate cancer and administered both an MRI scan and a PSMA PET/CT scan, with the images that suggested cancer being followed up by a biopsy. In a total of 240 patients recruited, MRI scans identified abnormalities in 141 whereas PSMA PET/CT identified abnormalities in 198. Following this analysis 181 patients underwent a prostate biopsy with 82 subsequently found to have clinically significant prostate cancer.

Analysis demonstrated that the MRI scans were significantly more accurate at detecting prostate cancer of any grade compared with PSMA PET scans (0.75% versus 0.62%). However, when looking at only clinically significant prostate cancers, there was no significant different in accuracy.

“This study confirms that the existing ‘gold standard’ of pre-biopsy detection, the MRI, is indeed a high benchmark. Even with fine-tuning, we suspect PSMA PET/CT won’t replace the MRI as the main method of prostate cancer detection. But it will likely have application in the future as an adjunct to the MRI, or for people for whom an MRI is unsuitable, or as a single combined 'diagnostic and staging' scan for appropriately selected patients,” explained Head Researcher Lih-Ming Wong, St Vincent’s Hospital, Melbourne, Australia.

The researchers highlighted the importance of further research exploring PSMA PET/CT use in understanding cancer aggressiveness and avoiding unnecessary biopsy and treatment in the future. ●

"This study confirms that the existing ‘gold standard’ of pre-biopsy detection, the MRI, is indeed a high benchmark."

Increased Overall Survival Following Bladder Surgery Removal

PATIENTS who are positive for circulating tumour DNA (ctDNA) show a significant improvement after taken the immunotherapy drug atezolizumab, according to data presented at EAU22.

Comprising of DNA fragments and tumours that are shed and found in the bloodstream, ctDNA has emerged as a minimally invasive, potentially promising biomarker in clinical oncology. However, it is not used as standard detection as is involves tumour-specific sequencing for individual patients, which is costly and time-consuming.

The IMvigor010 trial investigated whether atezolizumab improved survival prospects when given to patients following bladder removal surgery for up to 1 year. Comparing individuals who had atezolizumab for 1 year with those who were placed in an observational group and received no further treatment, the researchers discovered that there no significant difference in overall survival.

Part of the trial, however, was to investigate the patients' ctDNA, which was measured after surgery and during treatment or observation. The researchers discovered that a subgroup of patients who were ctDNA-positive showed marked improvement after taking atezolizumab, having a significantly highly disease-free and overall survival than the observation group. Furthermore, patients who were ctDNA-positive and had become ctDNA-negative after treatment with atezolizumab had a particularly good prognosis.

While well known that patients who are ctDN-positive have a poor prognosis compared with those who are ctDNA-negative, this study shows, for the first time, that immunotherapy can change the course of the disease depending on ctDNA status. Morgan Rouprêt, Chairman of the European Section of Onco-Urology of the EAU (ESOU), believes that personalised medicine is "just around the corner," stating that ctDNA analysis is "relatively easy to do with new technology and it means we can select a subset of patients who are likely to respond."

> **"The researchers discovered that a subgroup of patients who were ctDNA-positive showed marked improvement after taking atezolizumab."**

Due to these results, this trial has been redesigned into the IMvigor011 study. This new trial will further evaluate ctDNA sampling in 500 patients who are ctDNA-positive, comparing atezolizumab against placebo after bladder removal surgery. ●

Let's Take a Look at the Very Best of EAU22: Great Topics, Great Research, and Great Teamwork

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The European Association of Urology (EAU) delved into the very latest in urological science at the 37th Annual Congress, EAU22, on 1st–4th July in Amsterdam, the Netherlands. The four days were filled to the brim with 2,580 presentations by more than 900 speakers, and 56 courses organised by the European School of Urology (ESU). This included six Game Changing sessions, a day of live surgery, eight plenary sessions, Section meetings, Urology Beyond Europe, poster presentations, prestigious awards, patient days, and industry sessions. EAU Nurses (EAUN) also held EAUN22 during this time.

The congress attracted over 8,200 participants from 124 countries, with some also opting to participate via the virtual option. The opening night not only honoured pioneering and promising urologists, it also commemorated the beginning of the 50th celebratory year of the EAU. Secretary General Frans Debruyne was awarded a bronze bust to mark his extraordinary contributions to the EAU during its 50-year existence.

EARLY BIRD CATCHES THE WORM

Day 1 was set in motion at 07:30 a.m. with the delivery of four Game Changing sessions (Figure 1). James Catto gave his conclusions on the 'Effect of robot-assisted radical cystectomy with intracorporeal urinary diversion vs. open radical cystectomy among bladder cancer patients: a randomised clinical trial' (Figure 2). He stated that participants undergoing complete robotic radical cystectomy spent statistically significantly more time out of the hospital than those receiving open surgery.

Marc-Oliver Grimm shared his presentation on the 'Complications with open versus robotic-assisted partial nephrectomy (OpeRa) in patients with intermediate/high complexity kidney tumours'. He concluded that the 30-day complication rate (primary outcome) was numerically lower with robot-assisted partial nephrectomy than open partial nephrectomy.

Thomas Powles shared promising 30-month disease-free survival benefit with adjuvant pembrolizumab in KEYNOTE-564 study, and André Deschamps highlighted results from EUPROMS 2.0, the importance of active surveillance, and shared decision-making for the treatment of prostate cancer.

Figure 1: Christopher Chapple welcoming all the attendees to the Annual European Association of Urology (EAU) 2022.

VISIBLE HAEMATURIA CASE

Plenary Session 1 began with Teele Kuusk introducing a patient case of a 58-year-old female with a small renal mass centred on bilateral cT1 in her presentation, 'Challenges in renal cancer'. This was followed by expert lectures on various treatment approaches and sequences addressing the case.

Alessandro Volpe said that renal tumour biopsies (RTB) can support treatment decisions for cT1 renal masses. In his presentation 'When do we perform biopsy?', he stated that the added value of RTBs is significant in the setting of bilateral tumours, especially in older patients and patients with less than three renal masses.

In addition, RTBs are safe and should be proposed especially when different treatment approaches, including active surveillance, are reasonable options. Volpe added that genetic and molecular characterisation beyond traditional histology on RTBs will have the potential to further optimise patient decision making.

Figure 2: James Catto delivering a session on the effect of robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy among patients with blood cancer.

VIRAL CONCERNS

The lessons we have learnt during the COVID-19 pandemic, including its impact on urological care, as well as urological research, and a call to action in the elimination of human papillomavirus (HPV)-related cancers, are some of the topics that were covered during Plenary Session 2. Experts Oscar Brouwer and Florian Wagenlehner chaired this highly informative session.

In his presentation 'Large simple trials after the COVID-19 pandemic: lessons learnt for urology research', Kari Tikkinen discussed the need for better evidence-based research. His take home message was: "Trials need to be as large as possible, as simple as possible, practical with minimal trouble, and deliver patient important outcomes."

Daniel Kelly, Co-Chair of the European Cancer Organisation (ECO) HPV Action Network, delivered his pre-recorded lecture on 'Eliminating HPV-related cancers: a call to action'. "HPV is largely preventable, yet it is the fourth most common cancer in some areas of Europe. We need to all be involved, and urologists have a role to play in HPV prevention, not just in dealing with the consequences," he said.

LIVE SURGERY AND LIVELY DEBATE

Day 2 had a strong surgical theme, beginning with the 'Nightmare Session', which presented several challenging cases during Plenary 3. Of note was the case of a ruptured kidney tumour, and the intense debate proceeding this between Andrea Minervini and medical lawyer Bertie Leigh. This was an in depth and thought-provoking cross-examination.

In the afternoon, the 'Meeting of the EAU Section of Uro-Technology (ESUT) in cooperation with ERUS and EULIS' (the EAU Sections of Robotic Urology and Urolithiasis, respectively), held a 7-hour 'live surgery session', which is always a highlight at every Annual Congress (Figure 3A and 3B).

Patricia Zondervan demonstrated a 3D laparoscopic radical nephrectomy on a 'sticky' older female patient, leading to some discussion with the panel on the choices of her approach and also her preference for 3D laparoscopy, even for radical nephrectomy: "Especially combined with 4K, I find 3D offers a clear advantage over 2D."

The eURO Auditorium then switched focus to Henk Van Der Poel and his robotic-assisted prostatectomy with sentinel lymph node mapping. The use of indocyanine green under near-infrared light, combined with radioactive tracer and the Crystal Probe (Cygnus Instruments, Dorchester, UK) device made it a relative breeze to find the sentinel nodes.

STATE-OF-THE-ART LECTURES

The presentation 'Landscape of current trials with intravesical treatment in high-risk BCG [Bacillus Calmette–Guérin]-naïve NMIBC [non-muscle invasive bladder cancer]' by Ashish Kamat kickstarted Plenary Session 4. During his lecture, he underscored that for the purpose of clinical studies, all high-grade tumours should be considered high-risk. "This is not to take away from the EAU Guidelines classification, which is good for counselling patients," said Kamat.

In his lecture 'Lynch syndrome: what urologists need to know', Morgan Rouprêt stated that Lynch syndrome is the most common familial cancer syndrome, first described by Aldred Warthin in 1895.

In identifying Lynch syndrome in patients, Rouprêt mentioned the

Figure 3A: Live and lively debate on Day 2 of European Association of Urology Congress (EAU) 2022.

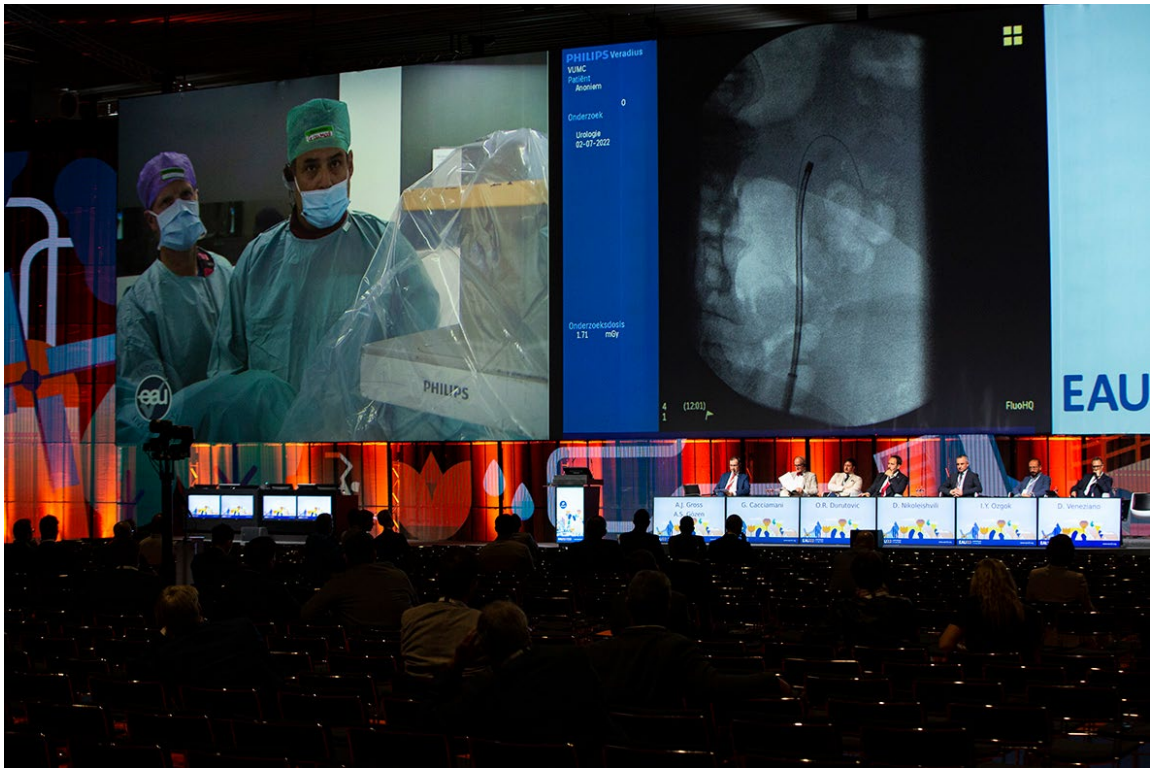
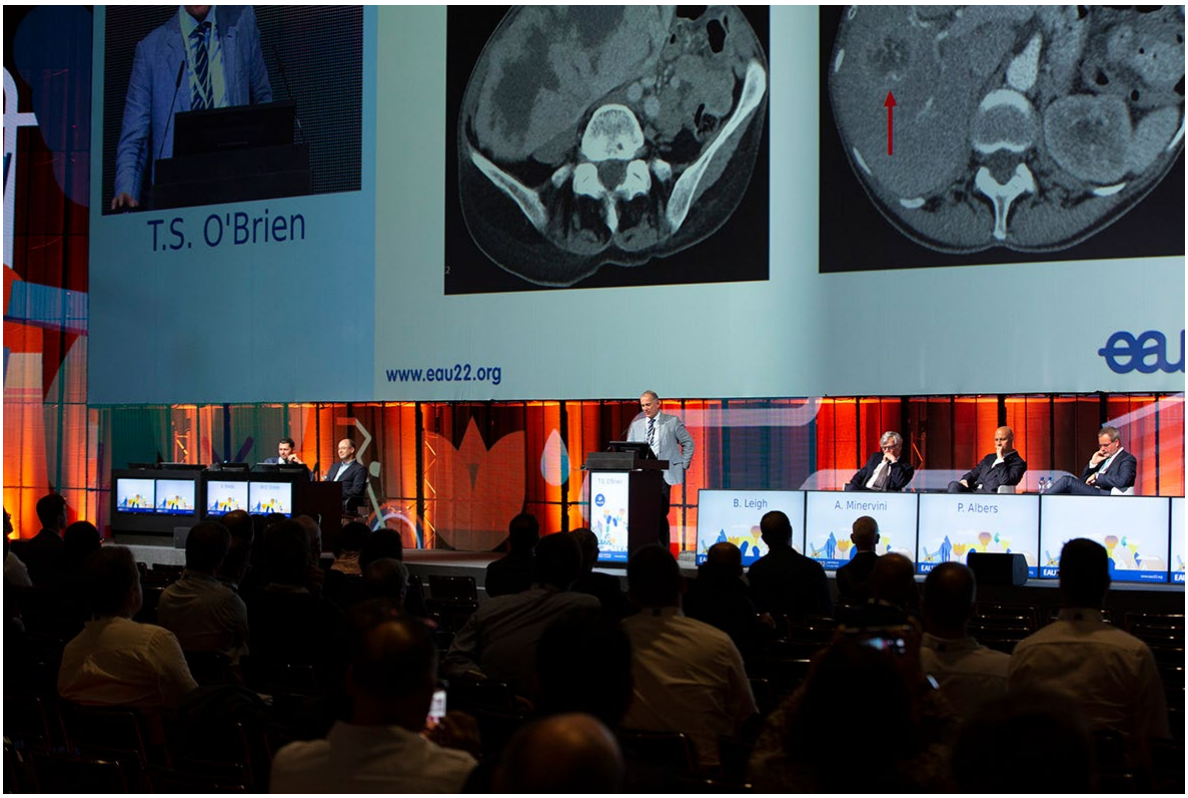


Figure 3B.



Bethesda criteria to test tumour for microsatellite instability, which included colorectal cancer in a patient who is younger than 50 years old, and presence of synchronous or metachronous syndrome-associated tumours regardless of age, to name a few. In addition, he mentioned the Amsterdam criteria, which involved a patient's three relatives with a Lynch syndrome-associated cancer (e.g., colorectal cancer, endometrial, etc.), wherein one is a first-degree relative of the other two, and at least two successive generations are affected; and other indicators.

MORE BREAKING NEWS

Day 3 began with several Game Changing presentations. On behalf of his team, Declan Murphy shared encouraging initial trial results for LuTectomy, stating: "Neoadjuvant Lu-PSMA is safe, effective, and surgery is very straightforward". The session followed with Steven Joniau presenting updates on the ARNEO trial in 'Randomised Phase II trial of neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for unfavourable intermediate- and high-risk prostate cancer'. He concluded that degarelix plus apalutamide achieved better tumour response, PSMA PET SUVmax after neoadjuvant therapy predicts pathological response, and phosphatase and tensin homologue loss is a negative predictor of minimal residual disease.

HOW USEFUL IS MRI?

There were plenty of scientific updates and even more lively debate in Plenary 5

on high-risk local treatment for prostate cancer. Experts Alberto Bossi and Alberto Briganti chaired this highly informative morning.

In Giorgio Gandaglia's state-of-the-art lecture 'How does MRI change the local strategy in high-risk men? – Surgery', he stated that MRI in high-risk patients is important to provide the prognostic information to guide the delivery of tailored surgical approaches; to identify nerve-sparing candidates; and to identify patients who should receive wider excision.

According to Gandaglia, MRI does have an impact on changing surgical plans in the rising risk category by up to 52%, and the surgical decision-made based on MRI was correct on average in 91% of the high-risk group.

NEW MINI-SLING TRIAL RESULTS

During a Game Changer session Mohamed Abdel-Fattah presented the recent results of the Single Incision Mini-Slings versus Standard Synthetic Mid-Urethral Slings in the Surgical Management of Stress Urinary Incontinence in Women (SIMS RCT). The percentage of patients reporting success remained similar in the two groups at the 3-year follow-up. The trial will continue up to the 10-year mark.

At discussion time, Chris Chapple made it clear that that the results of the trial were welcomed. Chapple complimented the trial as "the benchmark in a market where slings are introduced with little or no research or trials."

Delegates then had an update on the ALTAR trial from Christopher Harding with his Game Changer presentation 'Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial'. He concluded that non-antibiotic prophylactic treatment with methenamine hippurate might be appropriate for women with a history of recurrent episodes of urinary tract infections, informed patient preferences, and antibiotic stewardship initiatives, given the demonstration of non-inferiority to daily antibiotic prophylaxis seen in this trial.

Plenary Session 6 covered the topic of personalised surgical management of lower urinary tract symptoms and benign prostatic obstruction, which included lectures on all of the available surgical options from resection to vaporisation, and novel techniques like the temporarily-placed urethral opening system. The session ended with a panel discussion between the 11 experts, weighing the merits of the huge variety of approaches available to urologists in 2022.

UPDATES ON PROPEL AND ARASENS TRIALS

Noel William Clarke launched Game Changing Session 5 with his lecture 'Exploratory endpoints from PROpel: a Phase III trial of abiraterone + olaparib vs. abiraterone + placebo in 1st line metastatic castration-resistant prostate cancer', wherein he provided the findings of the trial.

In the next presentation, 'Overall survival (OS) by circulating tumour DNA (ctDNA) status in patients with post-operative muscle-invasive urothelial carcinoma (MIUC) treated with atezolizumab (atezo): update from IMvigor010', Jürgen Gschwend shared that with longer follow-up since the interim analysis, ctDNA-positive status continued to identify patients at high risk of relapse who have improved overall survival with atezolizumab in contrast to observation.

The 'Overall survival with darolutamide versus placebo in combination with androgen-deprivation therapy and docetaxel by stratification factors in

the Phase 3 ARASENS trial' update was presented by Bertrand Tombal, and the 'Phase III study comparing diagnostic accuracy of mpMRI prostate to 18F-DCPyL PSMA PET/CT' results were shared by L.M. Wong. He stated that multi-parametric MRI of the prostate remains first line for now, and has a better diagnostic accuracy to detect any prostate cancer.

ALL FACETS OF STONE SURGERY

Some of the stone-related topics covered in Session 8 were the use of access sheaths in children, devising the 'perfect' algorithm for a follow-up schedule for stone disease, and several case discussions that served to highlight different approaches and different instruments.

A potentially promising new technology was presented by Jonathan Harper, the burst wave extracorporeal shock wave lithotripsy, which uses ultrasound pulses instead of shock waves. This new technology might allow for shorter and in-office procedures. The first careful conclusions from Harper, based on the initial series of in-human tests, were that comminution was effective with only minimal safety concerns, and that the treatment was well-tolerated and effective.

EAU SPECIALITY SESSION: 'THE BEST OF EAU22'

On the afternoon of Day 4, an EAU Specialty Session on the 'Best of EAU22' was held, with a panel of experts sharing condensed summaries on 11 topics covering important research and data. This gave delegates an opportunity to a highly concentrated dose of the EAU22 scientific programme.

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Urolithiasis: Updated Guidelines

Author:	Carlotta Zennaro, Editorial Assistant

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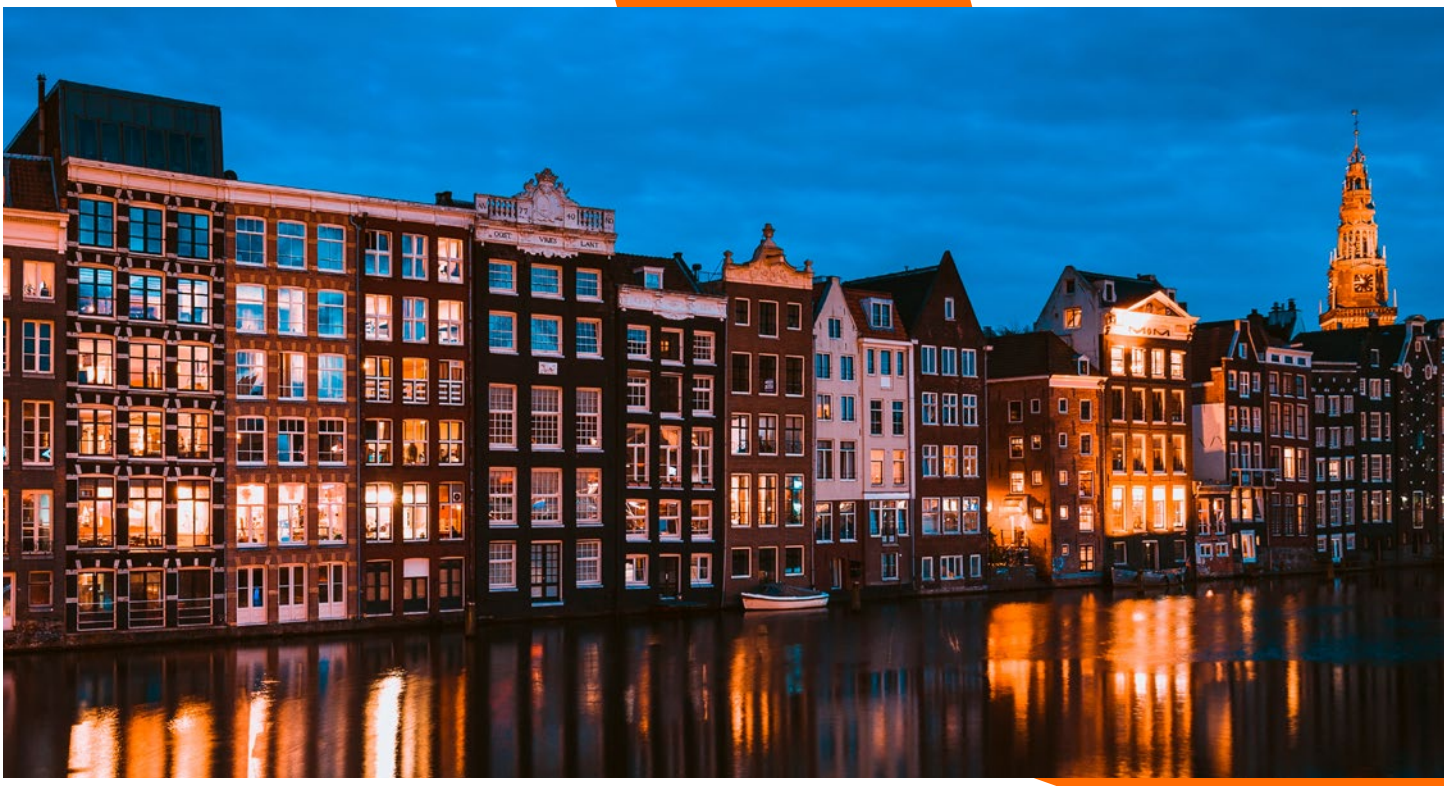
THE EUROPEAN Association of Urology (EAU) hosted a thematic session on Day 4 of its 37th Annual Congress where three experts discussed the state-of-the-art guidelines on urolithiasis treatment. The experts shared the latest research and their own clinical experience and suggested improvements to the current treatment guidelines, with a focus on protection from radiation exposure for both patients and practitioners, as well as on the effectiveness of pharmacological prophylaxis for high-risk patients.

RADIATION PROTECTION DURING ENDOUROLOGY

The first speaker, Andreas Skolarikos, Professor of Urology, National and Kapodistrian University of Athens, Greece, gave an informative lecture on the importance of effective radiation protection during endourological procedures. As the use of fluoroscopy has become an increasingly popular method to guide these minimally invasive operations, a clear understanding of what radiation side effects are, where radiation comes from, and who should be protected is crucial. Current guidelines use the 'as low as reasonably achievable' principle, to ensure that exposure levels remain below the accepted limit. Annually, maximum levels of occupational effective dose limits are 5,000 rem/year for the whole body, 15,000 mrem/year for the lens of the eye, and 50,000 mrem/year for the thyroid in adult patients. Personnel, urologists, and patients are subjected to radiations either as direct radiation, or as scatter radiation from the patient for the medical personnel present in the suite and should therefore all be protected.

Skolarikos highlighted the ways in which radiation exposure can be reduced for patients. Firstly, it is vital to lower magnification, as the greater the magnification, the greater the radiation exposure. Secondly, studies suggest that pulsed fluoroscopy should be used in place of continuous fluoroscopy. Skolarikos shared the results of his own team, which demonstrated that when pulsed fluoroscopy is employed in combination with collimated fluoroscopy the scatter radiation is lowered by five-fold.[1] Additionally, the field overlap should be minimised, as using the lateral position of the c-arm significantly increases radiation exposure. Finally, Skolarikos stressed that digital acquisitions should be avoided, and practitioners should instead rely on the last image hold.

Radiation protection for urologists is predominantly available in the form of structural, mobile, or personal shielding. Personal shielding, including lead aprons, thyroid collars, glasses, and gloves, has been proven extremely effective: sensitive areas such as the gonads benefit from 80% protection, while the bone marrow is protected 90.0–90.5%. Furthermore, the X-ray should be close to the patient and should be positioned underneath the patient's body to help decrease scatter radiation. Medical staff should also



keep the distance from the c-arm, use the quicker dilation method for percutaneous nephrolithotomy to reduce exposure, and measure their own exposure levels every month with a dosemeter to ensure the dose of radiation received remains below the acceptable limits.

MEDICAL PROPHYLAXIS IN THE HIGH-RISK PATIENT: TEMPORARY VERSUS LIFELONG

The next speaker was Giovanni Gambaro, Professor of Nephrology, University of Verona, Italy, who discussed the pharmacological prophylaxis in high-risk patients. Opening his lecture, Gambaro emphasised the importance of having a well-defined description of who high-risk patients are in order to correctly determine who might require lifelong medical prophylaxis.

Gambaro firstly identified recurrent stone formers as belonging in the high-risk category, with only 45% of patients recurring in 10 years and only 30% recuring in 5 years, and within that timeframe only 10–15% recurring more than three times.[2] As there is no biomarker or algorithm to determine which patients might truly be recurrent stone formers, it becomes necessary to rely on observation alone. Furthermore, certain types of stones are associated with high risk of recurring and damaging the kidneys; these types of stones include cystine, brushite, struvite, and uric acid stones.

Moreover, those with other clinical risks associated with stones are also categorised as high-risk patients. For instance, conditions such as primary and secondary hyperoxaluria, neurological bladder, distal renal tubular acidosis, or anatomical abnormalities of the kidneys and urinary tract are all linked with a higher risk of acute and/or chronic renal failure. Patients with medullary sponge kidney, primary hyperparathyroidism, malabsorptive syndromes, as well as certain genetic conditions are also in the high-risk group as they show increased risk of developing metabolic bone disease.

Finally, certain professions are included in this category, such as aircraft pilots, surgeons, and any other profession linked with infrequent voiding syndrome.

Gambaro concluded by reiterating that all these factors, including previous history of stones, associated risks to the bones and kidneys, and professional occupation, should be evaluated to identify high-risk patients who might require lifelong pharmacological prophylaxis.

WHAT IS NEW IN THE UROLITHIASIS GUIDELINE?

The final speaker of the thematic session was Robert Geraghty, Urology Registrar, Freeman Hospital, Newcastle upon Tyne, UK, who presented the updated urolithiasis guidelines. Four separate sections were incorporated in the new urolithiasis guidelines: best clinical practice in urinary stone intervention, a new section on radiation exposure, new diagnostic algorithms, and new follow-up algorithms.

Firstly, new sections detailing the best clinical practice for preoperative management of urolithiasis were included, as well as for the three most commonly performed procedures for stone disease, namely shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy.

"Previous history of stones, associated risks to the bones and kidneys, and professional occupation, should be evaluated to identify high-risk patients who might require lifelong pharmacological prophylaxis."

Secondly, the new section on radiation exposure delineates the risk for both patients and staff. Geraghty discussed evidence of a study on atomic bomb patients demonstrating that the risk of malignancy from ionising radiation is both age and dose dependent; this data led to the recommendation to minimise the use of ionising radiation in stone formers, especially in patients with recurring disease. Furthermore, with the maximum annual occupational

exposure being 50 mSv, the guidelines state that all the necessary personal protective equipment should always be worn while performing endourological procedures, consisting of lead aprons, thyroid shield, and lead glasses. Access to fluoroscopy for guidance remains mandatory in endourology, as there is limited evidence on the effectiveness of fluoroscopy-free operations, especially when considering complex cases.

"Four separate sections were incorporated in the new urolithiasis guidelines: best clinical practice in urinary stone intervention, a new section on radiation exposure, new diagnostic algorithms, and new follow-up algorithms."

Geraghty presented the two new diagnostic algorithms introduced in the urolithiasis guidelines. The novel calcium oxalate diagnostic algorithm for high-risk stone formers can be used in conjunction with the pre-existing algorithm on risk stratification. This algorithm aims to help differentiate particular causes of calcium oxalate stone formation in high-risk patients who have had a 24-hour urine collection to allow for the development of targeted therapies. Similarly, the uric acid stone diagnostic algorithm for high-risk stone formers was also introduced, with the goal of differentiating causes of uric acid stone formation in high-risk patients who have had a 24-hour urine collection to allow for the development targeted therapies. Geraghty emphasised that uric acid stones are high risk stones by themselves, so all patients with a uric acid stone should be having a 24-hour urine collection.

Finally, a section on new follow-up algorithms was included in the urolithiasis guidelines as there was unclear guidance on follow-up of stone patients. Consequently, the panel undertook a systematic review and meta-analysis of all available literature on follow-up. Unfortunately, there was a lack of high-quality data; therefore, the panel agreed on a series of consensus statements regarding follow-up using the data from the review. Evidence gathered from the review and meta-analysis showed that for high-risk patients the data was particularly heterogeneous. For those on medical treatment, 75% of patients remained stone-free after 5 years, while for those not on prophylaxis the figure dropped to 56% after 5 years. However, given the poor data, the panel advises lifelong follow-up for these patients. ●

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Improvements in Prostate Cancer Management: Focus on Imaging and Treatment

This article details improvements in imaging techniques in prostate cancer as discussed in a Telix Pharmaceuticals-sponsored symposium delivered as part of the European Association of Urology (EAU) 37th Annual Congress held in Amsterdam, the Netherlands, between 1st–4th July 2022

Chairpeople:	Alicia Morgans[1]
Presenters:	Stefano Fanti,[2] Jochen Walz,[3] Alicia Morgans[1] 1. Genitourinary Medical Oncologist/Medical Director, Survivorship Program, Dana-Farber Cancer Institute, Boston, Massachusetts, USA 2. Professor of Diagnostic Imaging/Director, Nuclear Medicine Division and PET Unit, S. Orsola Policlinic Hospital, Bologna, Italy 3. Professor of Urology/Head, Department of Urology, Institut Paoli-Calmettes Cancer Centre, Marseille, France

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Meeting Summary

Prostate cancer has traditionally been staged through the use of conventional imaging techniques such as bone scintigraphy, CT, and MRI. However, the introduction of more sensitive techniques, such as prostate-specific membrane antigen (PSMA) imaging, has allowed previously undetectable metastases to be identified, thereby enabling more accurate staging of the disease and greater refinement in management strategies.

This article summarises a symposium delivered on 3rd July 2022 at the 37th European Association of Urology (EAU) Annual Congress in Amsterdam, the Netherlands, where speakers from three different specialties raised important questions in prostate cancer imaging. Stefano Fanti, Professor of Diagnostic Imaging/Director from S. Orsola Policlinic Hospital, Bologna, Italy, asked: "What is PSMA all about?", and Jochen Walz, Professor of Urology and Head, Department of Urology at the Institut Paoli-Calmettes Cancer Centre, Marseille, France, wondered: "When does PSMA help me?" Alicia Morgans, Genitourinary Medical Oncologist/Medical Director at the Dana-Faber Cancer Institute, USA, then offered an overview of the future of prostate cancer management. The session concluded with the presentation of three cases of patients with different stages of prostate cancer, all of which illustrated the transformative benefit of PSMA imaging in accurately staging patients and directing subsequent treatment options.

Introduction

Imaging has a pivotal role in the staging of primary prostate cancer, as well as in determining optimal management strategies.[1] Conventional imaging modalities used in prostate cancer have traditionally included CT, MRI, and ^{99m}Tc-labelled bisphosphonate bone scintigraphy.[2] Although widely available, these modalities have significant limitations, including poor sensitivity and specificity for metastatic disease.[3] A desire to find a better diagnostic imaging technique for prostate cancer led to a focus on prostate-specific membrane antigen (PSMA), which is highly overexpressed in most prostate carcinoma cells.[1] Since its introduction in 2011, PET imaging with agents targeting PSMA has demonstrated value in the staging of recurrent prostate cancer, and has increasingly been adopted in clinical practice.[1] The most widely studied PSMA radioligand is ^{68}Ga-labelled PSMA-11 (^{68}Ga-PSMA-11 [ABX Advanced Biochemical Compounds GmbH, Radeberg, Germany]).[2,4]

In the Telix-sponsored symposium, 'Improvements in prostate cancer management: focus on imaging and treatment', delivered on 3rd July 2022 at the 37th EAU Annual Congress in Amsterdam, the Netherlands, speakers from three different specialties invited delegates to 'get on board the PSMA train' to optimise the imaging and treatment of prostate cancer, and help improve outcomes for patients.

What Is Prostate-Specific Membrane Antigen All About?

Stefano Fanti

Fanti opened the symposium by asking: 'What is PSMA all about?' He explained that PSMA is a unique membrane-bound glycoprotein that is overexpressed in prostate cancer as well as the neovasculature of most solid tumours, but is not expressed in the vasculature of normal tissues.[5] Fanti described how this overexpression makes PSMA an important marker in solid tumours, including (but not only) prostate cancer.[6] PSMA expression is higher in high-grade and castration-resistant prostate cancer (CRPC) than in less advanced forms of the disease.[7]

The small molecule inhibitor of PSMA, ^{68}Ga-PSMA-11, binds with high affinity to the enzymatic pocket of PSMA, where it remains trapped within the prostate cancer cell.[8] Use of the PSMA tracer with PET/CT allows functional imaging of the body to identify localised 'hotspots' of prostate cancer.

Performance

Fanti explained that the performance of an imaging technique may be described in terms of its sensitivity and specificity. Data from one of the first large meta-analyses of ^{68}Ga-PSMA PET showed that this technique was effective in detecting metastases in patients with biochemical recurrence of prostate cancer, and had favourable per-node sensitivity (75%) and specificity (99%).[4] The value of PSMA PET

scanning for disease staging is now reflected in guidelines on the evidence-based management of prostate cancer.[9]

Fanti next compared ^{68}Ga-PSMA-11 with other tracers for the imaging of patients with prostate cancer. One study of patients with biochemical recurrence of prostate cancer and low prostate-specific antigen (PSA) levels (<2 ng/mL) after radical prostatectomy who underwent both ^{18}F-fluciclovine and PSMA PET/CT scans within 15 days of each other demonstrated the clear superiority of ^{68}Ga-PSMA-11 in terms of the biochemical recurrence detection rate.[10] This study was unusual in that the same patients were imaged with both techniques, and supports the positioning of PSMA as the PET tracer of choice in this setting. Data from a systematic review of 98 individual studies examining the role of imaging in early recurrent prostate cancer also demonstrated a higher detection rate for ^{68}Ga-PSMA-11-based imaging compared with any other imaging modality, including CT or MRI.[11]

Reliability

Fanti noted that although PSMA PET is the most accurate and sensitive method for detecting the biochemical recurrence of prostate cancer, issues remain in terms of reliability. He explained that if a patient has recently been treated with radiotherapy or brachytherapy, inflammatory changes may induce local uptake of the tracer that could be misinterpreted as metastatic disease. An experienced physician would understand that a solitary faint signal in a rib does not necessarily indicate pathological changes.[12] Further, any risk of misinterpretation could be mitigated through a judicious choice of PSMA tracer, with the onus being on the nuclear medicine physician to select the most appropriate tracer for a given situation. For example, data suggest that in patients with biochemical recurrence of prostate cancer, ^{18}F-PSMA-1007 (ABX Advanced Biochemical Compounds GmbH, Radeberg, Germany) may be suitable for the detection of locoregional lesions near the urinary tract, whereas ^{68}Ga-PSMA-11 may be a better option for the identification of distant metastases such as those in bone.[13] Another study showed that ^{68}Ga-PSMA-11 PET/CT gave fewer false positives than ^{18}F-PSMA-1007 PET/CT in patients with biochemical recurrence of prostate cancer after radical prostatectomy (Figure 1).[14]

Fanti commented that "if the [aim] in biochemical recurrence is to find possible sites of metastases at the bone level, it is clear I would favour ^{68}Ga-PSMA-11 over ^{18}F-PSMA-1007."

Fanti concluded by noting that PSMA PET has been a fantastic success in prostate cancer imaging, but that the optimal use of this technique is all about the choice of tracer. He advised that tracer selection should not be made on the basis of cost or availability, but should be based on the performance, robustness, and reliability of the tracer in question.

When Does Prostate-Specific Membrane Antigen Help Me?

Jochen Walz

In order to answer the question, "when does PSMA help me?", Walz began by setting out the different clinical scenarios in which PSMA imaging can be used, including initial staging after diagnosis, staging in patients with persistent PSA after radical prostatectomy, and staging at the time of biochemical recurrence or disease progression.

Initial Staging

Walz first described the ProPSMA study in which ^{68}Ga-PSMA-11 PET/CT outperformed conventional imaging in males with biopsy-proven prostate cancer and high-risk features in terms of accuracy, specificity, and sensitivity, with particular sensitivity in the lymph nodes.[15]

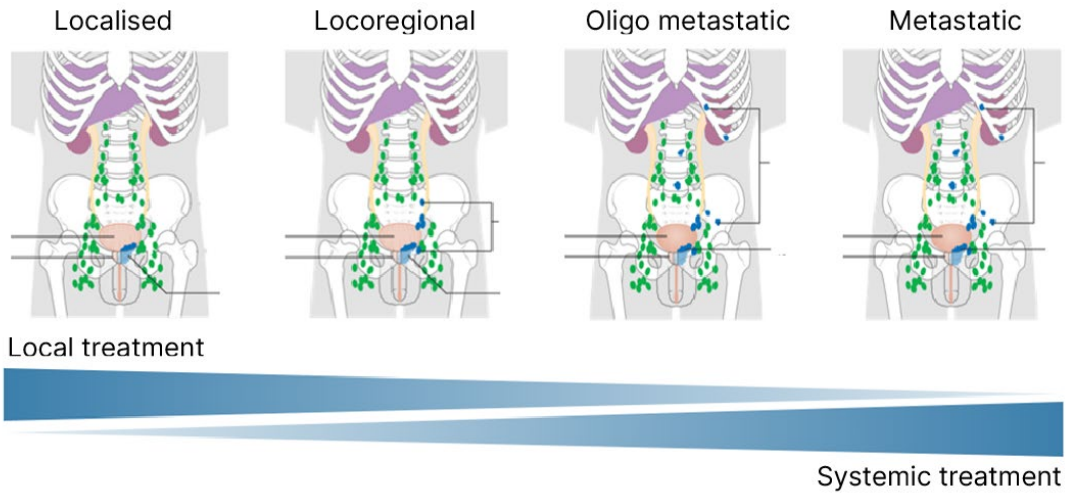
Walz next introduced the concept of 'stage migration', in which a more sensitive imaging tool allows the true position of a patient along the prostate cancer spectrum to be determined (Figure 2).[16,17] This approach may help to identify the optimal balance between local and systemic therapies and thereby improve patient outcomes. In the absence of available data to understand how this information may be used in practice to change disease management, Walz explained that patients currently need to rely on expert opinion to direct treatment based on PSMA PET.[9,18]

Figure 1: Distribution of suggestive and benign lesions for all PSMA-ligand–positive lesions on 68Ga-PSMA-11 PET/CT and 18F-PSMA-1007 PET/CT.

Adapted from Rauscher et al.[14]

PCa: prostate cancer; PSMA: prostate-specific membrane antigen.

Figure 2: Spectrum of prostate cancer.



Staging in patients with persistent PSA after radical prostatectomy.

Adapted from two images[16,17] *by Cancer Research UK (2015) under the terms of the Creative Commons Attribution -ShareAlike 4.0 International (CC BY-SA 4.0) licence, via Wikimedia Commons.*

Walz described how treatment options vary according to the region of the body in which the prostate cancer persists. For example, local persistence in the prostatic bed and regional persistence in the pelvic lymph nodes are both potentially curable with regional salvage treatment, while distant or systemic persistence in the lymph nodes or bone requires systemic treatment.

Patients with PSA persistence have a higher risk of disease progression at 15 years compared with those with an undetectable PSA.[19] PSMA imaging in patients with persistent PSA often

detects pelvic lymph node metastases outside the standard field, in the obturator, presacral, or mesorectal nodes.[20,21] PSMA imaging, therefore, helps to stage these high-risk patients and direct whether local or systemic treatment is required. Even in patients with early PSA persistence (0.1–0.2 ng/mL), PSMA imaging can help locate disease.[21] Use of PSMA imaging in cases of persistent PSA after surgery is also recommended by the guidelines,[9] although there is currently uncertainty regarding the best treatment approach when PSMA PET or CT reveals metastatic disease.

Staging at Biochemical Recurrence or Progression of Prostate Cancer

Walz explained that an early understanding of whether rising PSA is due to local recurrence, locoregional recurrence, or systemic recurrence is highly beneficial, as it allows early intervention with the most appropriate treatment. PSMA imaging is able to detect lesions even in patients with low PSA levels (>0.2 ng/mL).[4]

Emerging data suggest that new imaging approaches are improving the treatment of patients and guiding the use of post-prostatectomy salvage radiotherapy,[22] salvage lymph node dissection,[23] and metastasis-directed therapy.[24]

Walz noted that it is not completely clear how clinicians should act on the information provided by PSMA imaging in this setting, and again need to rely on expert recommendations until further data become available.[18] It is important, Walz concluded, that "care should be taken to avoid unproven treatment decisions that may result in under-treatment (or over-treatment), and finally harm to patients."[25]

The Future of Prostate Cancer Management

Alicia Morgans

Morgans concluded the formal presentations by identifying forward-thinking clinical applications of advanced imaging that might provide the greatest benefit to patients with prostate cancer.

Defining New Disease States

Echoing an earlier point from Walz, Morgans noted that it is critical to treat patients with the right therapies based on their stage migration, and that the use of PET imaging for high-risk localised disease allows the identification of metastatic lymph nodes that would not be visible on conventional CT or bone scans. Data from the STAMPEDE trial[26] show that intensification of androgen deprivation therapy (ADT) with abiraterone improves metastasis-free survival and overall survival in patients with clinically lymph node-positive disease or very high-risk localised disease.[27]

Morgans also showed data from the ORIOLE trial,[28] which demonstrated that stereotactic ablative radiation of all lesions visible on PSMA imaging may help to improve outcomes in patients with biochemical recurrence.[29] Finally, they described how PSMA imaging identifies previously undetectable metastases lesions in many patients (>98%) with non-metastatic CRPC based on conventional imaging.[30] Thus, PSMA imaging may help to guide a more accurate determination of stage migration, refine treatment options in the non-metastatic CRPC setting, and further improve outcomes, yet Morgans emphasised patients should still receive the intensified systemic treatment to prolong metastasis-free survival and overall survival.[30]

Selection for Treatment

Morgans next described the important role of PSMA-11 in identifying candidates for treatment with ^{177}Lu-PSMA-617 (Advanced Accelerator Applications, Saint-Genis-Pouilly, France) a radioligand recently approved by the U.S. Food & Drug Administration (FDA) for the management of metastatic CRPC. The VISION trial[31] showed that the addition of ^{177}Lu-PSMA-617 to standard therapy improved progression-free survival and overall survival in patients with metastatic castration-resistant cancer detectable by PSMA-11 imaging.[32] Morgans noted that effective therapies of this type are only made possible with the availability of suitable imaging agents such as PSMA-11.

Future Opportunities in Radioligand Therapy

Morgans concluded her presentation by introducing the novel radioligand, TLX591 (Telix Pharmaceuticals, Melbourne, Australia), which is a monoclonal antibody construct that binds with high affinity to PSMA with limited off-target effects. TLX591 has been shown to have clinical efficacy and an acceptable safety profile as a potential alternative to PSMA-directed small molecules (Figure 3).[33,34] Morgans suggested that this innovative therapeutic approach may offer new opportunities for patients with prostate cancer.

Patient Cases Discussion and Roundtable

Stefano Fanti, Jochen Walz, and Alicia Morgans

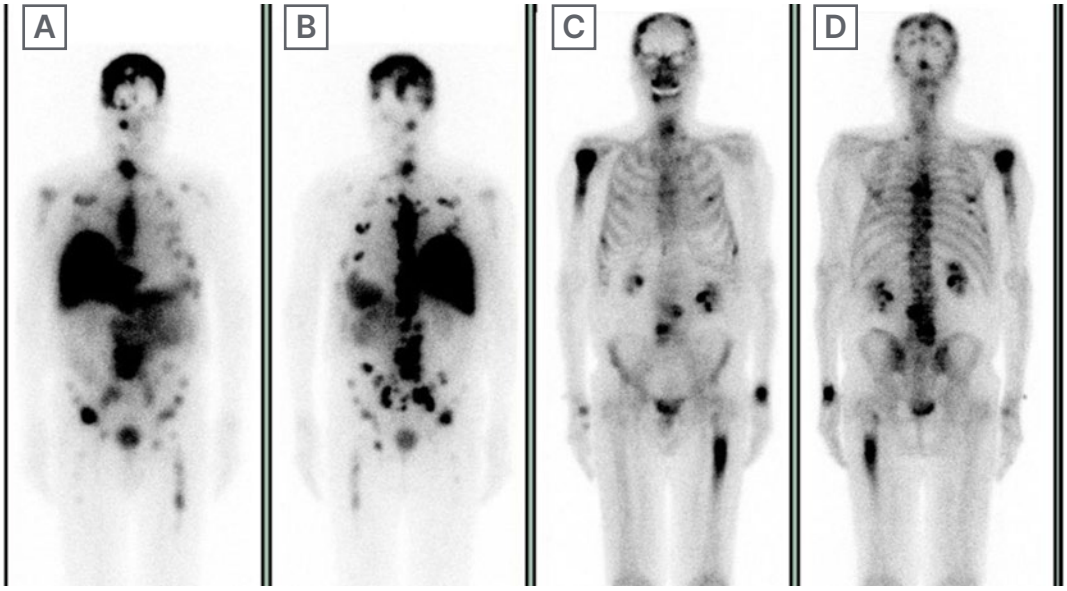
Following conclusion of the formal presentations, the panel members discussed three real-world case studies to illustrate the use of PSMA imaging in the settings described.

Case 1: Biochemical Recurrence (Hormone Sensitive)

Morgans presented the case of a 69-year-old male with a history of prostate cancer who was treated with a prostatectomy in July 2016. At the time of prostatectomy, he had a PSA of 7.2 ng/mL, and pT3a pN0 M0 R1 (positive right apical margin) prostate adenocarcinoma with a Gleason score of 4+4. Their PSA was undetectable within 6 weeks after surgery. They underwent adjuvant radiotherapy in September 2016, and then his PSA was monitored by a urologist. Their past medical history included hypertension controlled with hydrochlorothiazide, while their grandfather had had prostate cancer and their father had had heart disease. In April 2021, his PSA had risen to 0.3 ng/mL from 0.2 ng/mL in March 2021.

Walz noted that because this patient had already received adjuvant radiotherapy, there was no urgency to proceed with salvage therapy. Walz indicated that more information about PSA kinetics would be valuable. Walz also noted that the substantial length of time between the initial disease and the subsequent increase in PSA suggested that the disease may not be aggressive in nature.

Figure 3: Prostate-specific membrane antigen radiolabelling patient experience.



Data courtesy of Scott Tagawa.

PSMA: prostate-specific membrane antigen.

The patient's PSA increased further to 0.5 ng/mL in May 2021 and then to 1.2 ng/mL in August 2021. At this point, the patient underwent ^{68}Ga-PSMA PET imaging to gain additional information about the status of his recurrent disease.

PSMA imaging revealed intense uptake in the kidney, liver, and spleen as well as hotspots in the lower pelvis. However, Fanti explained that the sagittal view showed only superficial uptake in the skin in this area, most likely indicating tracer contamination rather than pathological changes. However, Fanti also highlighted two other focal hotspots corresponding to lymph nodes, which he would report as suspicious. He noted that such a relatively intense uptake, focally localised at the lymph node, would be very unlikely to be a false positive.

Walz agreed that this patient is likely to have a locoregional relapse, and would be a candidate for radiotherapy or a regional salvage treatment depending on what adjuvant therapy had been given previously. Walz concluded that several treatment options would be available for this patient and that these would in practice be discussed and agreed within a multi-disciplinary team.

Case 2: Staging High-Risk Localised Disease

In the second case, a 67-year-old male with a history of osteoarthritis was found to have a left-sided nodule following a digital rectal examination as part of his annual physical examination. Their PSA at this time was 13.8 ng/mL, and the patient felt well except for recent incidents of nocturia. The patient underwent a prostate biopsy that demonstrated Gleason 4+5=9 (Grade group 5) prostate adenocarcinoma in three of six cores on the left side and Gleason 3+4=7 (Grade group 2) prostate adenocarcinoma in two of six cores on the right side. The patient presented for further management of their high-risk localised prostate cancer and underwent a bone scan.

Fanti observed that the bone scan was negative as expected, given the low sensitivity of the modality, and observed that PSMA imaging rather than a bone scan would now routinely be performed in these high-risk patients. Walz agreed that as this is a true high-risk patient with high volume disease, determination of disease stage would be required using the most sensitive imaging technique available; ideally PSMA.

Fanti interpreted the PSMA PET scan by observing several hotspots, including two in the thorax corresponding to lymph nodes. He noted that in some patients, uptake in the lung could be due to permanent inflammation of the lymph nodes, possibly caused by smoking. However, Walz determined that the intensity of the uptake in this case, together with other PSMA PET findings, suggested metastatic disease. Morgans added that the CT scan for this patient was negative, confirming that a negative CT scan should not undermine the findings from a more sensitive PSMA scan.

Walz noted that additional scanning might be necessary to confirm that this patient requires systemic treatment. Walz would also request a biopsy of the lymph nodes in the chest. Fanti noted that in similar cases, a biopsy has frequently confirmed prostate cancer metastasis. This together with the presence of bone metastases detected by PSMA imaging makes it less likely that a biopsy would be performed. Walz agreed that a biopsy would be most important if the lung lesions were the only lesions that would make a difference to the treatment approach.

Case 3: Non-metastatic Castration-resistant Prostate Cancer

Walz presented the final case of a 64-year-old male with a history of prostate cancer (diagnosed in November 2018) who was treated with prostatectomy in January 2019. At the time of prostatectomy, they had a PSA of 11.6 ng/mL and pT3b pN0 M0 Gleason 4+4 prostate adenocarcinoma. The patient's PSA was 0.2 ng/mL 6 weeks after surgery, and they underwent salvage radiotherapy with ADT for 6 months in March 2019. While receiving ADT, his PSA increased from 1.6 ng/mL in October 2019 to 1.9 ng/mL in January 2020.

Morgans commented that these findings are suggestive of castration resistance and that they would request measurement of testosterone levels. They would also request a PSMA PET but feared that this patient was showing signs of aggressive disease.

The patient's PSA continued to rise from 2.00 ng/mL in February 2020 to 3.81 ng/mL in October 2020, with a doubling time of 8.6 months, and his testosterone level was <20 ng/dL (castrate level). A CT scan of the abdomen and pelvis with intravenous contrast and a technetium bone scan were both negative. Fanti noted multiple hotspots on the PSMA PET scan, including several bone and nodal lesions, which would be reported as suspect.

Morgans observed that 'non-metastatic' CRPC is only really non-metastatic according to conventional imaging, while newer imaging techniques typically reveal these patients to have metastases in reality. Morgans said that they would treat this patient systemically with an androgen receptor antagonist in addition to ADT, but not with additional radiotherapy given the number and location of the lesions. They noted that the patient outcome may have been improved if it had been evaluated at an earlier, hormone-sensitive stage.

Conclusion

The presentations in this symposium demonstrated the effectiveness of ^{68}Ga-PSMA-11 PET/CT in the detection of prostate cancer tumours compared with other imaging modalities, and highlighted the clinical settings in which this technique adds value. The speakers illustrated how ^{68}Ga-PSMA-11 PET scans can inform and potentially improve patient management and survival. It was also noted that this modality may be used to identify candidates for therapies such as PSMA-targeted radioligand therapies. Finally, the speakers demonstrated how novel radioligand therapeutics, including monoclonal antibodies, may offer new opportunities in the treatment of patients with prostate cancer. The symposium closed with the presentation of three case studies, which demonstrated the clinical utility of PSMA imaging in clinical practice, illustrating the value of this technique and providing insights into how PSMA PET imaging is having a transformative effect on the management of prostate cancer.

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Advancing Patient Care in the Evolving Prostate Cancer Treatment Landscape

This Bayer-sponsored symposium took place on 3rd July 2022 as part of the European Association of Urology 2022 (EAU22) in Amsterdam, the Netherlands

Chairpeople:	Bertrand Tombal[1]
Speakers:	Martin Bögemann,[2] Bertrand Tombal,[1] Christian Gratzke[3] 1. Institute of Experimental and Clinical Research, Université Catholique de Louvain, Belgium 2. Department of Urology, University of Münster, Germany 3. Department of Urology, University Hospital Freiburg, Germany

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Meeting Summary

Most prostate cancer cases present as localised disease at initial diagnosis but can progress in about a fifth of patients to castration-resistant prostate cancer (CRPC) within 5 years. A major concern for patients and physicians is the development of metastases, affecting quality of life (QoL), and reducing overall survival (OS). Treatment guidelines for the different stages of prostate cancer continue to be modified with the publication of clinical trial results. Currently, androgen receptor inhibitors (ARi) are used in the management of non-metastatic CRPC. Among these, explained Martin Bögemann, Department of Urology, University of Münster, Germany, darolutamide's unique structure means it causes minimal side effects, likely due to reduced blood-brain

barrier penetration, while also reducing the potential for drug-drug interactions, which is especially important for patients treated for comorbidities. Treatment of metastatic hormone-sensitive prostate cancer (mHSPC) depends on a variety of factors, including when metastases developed in the course of disease and their volume. Bertrand Tombal, Institute of Experimental and Clinical Research, Université Catholique de Louvain, Belgium, described the evolution of mHSPC therapy from androgen deprivation therapy (ADT) and surgical castration as the only available options, to the emergence of the chemotherapeutic docetaxel and androgen receptor pathway inhibition (ARPI). He explained the results of Phase III clinical trials of various combination approaches, with a combination treatment of docetaxel, ADT, and darolutamide showing promise for overall survival. Discussions are ongoing about which patients with mHSPC should receive this triple therapy approach. Christian Gratzke, Department of Urology, University Hospital Freiburg, Germany followed by describing how treatment decisions are made, including the role of imaging, with a case study of a patient with non-metastatic castration-resistant prostate cancer (nmCRPC), and another with mHSPC. A further panel discussion considered treatment options for various presentations of prostate cancer, and why one would be chosen over another. The panel concluded with a question and answer sessions that focused on when and why patients with prostate cancer are sent for genetic testing.

Non-metastatic Castration-Resistant Prostate Cancer: Improving Overall Survival and Time to Metastasis While Maintaining Quality of Life

Martin Bögemann

Prostate cancer varies at initial diagnosis and in its progression, with non-metastatic and metastatic presentations that may or may not respond to ADT (Figure 1).[1] A major concern for doctors and their patients is the development of metastases, which affects QoL and OS. Although 90% of prostate cancer cases present with localised disease at initial diagnosis, failure to respond to ADT, known as castration resistance, will develop in 10–20% of males with prostate cancer within 5 years of follow-up.[2,3] The majority (86%) of patients with metastatic castration-resistant prostate cancer (mCRPC) will have progressed from nmCRPC.[4]

The risk of annual all-cause mortality increases following progression from nmCRPC (16%) to mCRPC (56%).[4] Five-year survival also falls after development of bone metastases from 56% to 3%.[6] Bone metastases significantly reduce a patient's QoL and increase healthcare costs.[6-11] "It's very important to keep patients away from metastasis," said Bögemann.

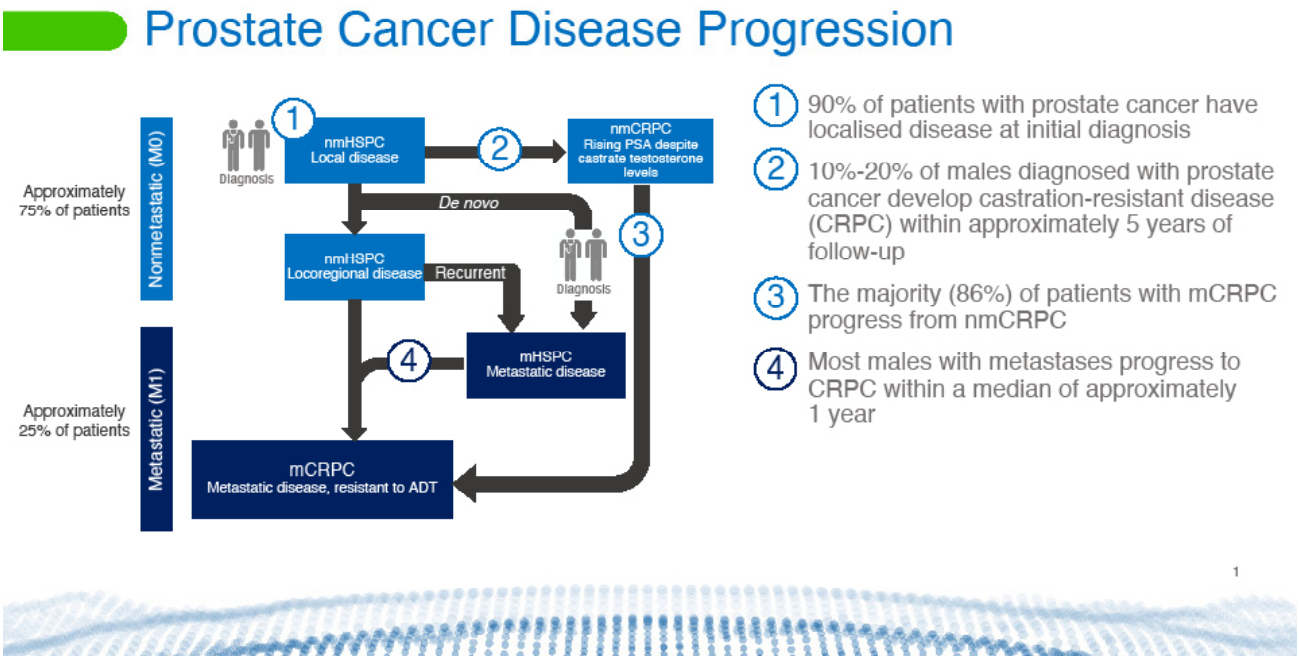
Bögemann's talk focused on treatment options for nmCRPC that can improve OS and time to mCRPC, while maintaining patients' QoL.

One thing clinicians look for in their patients with nmCRPC is the time it takes for the blood levels of a biomarker called prostate-specific antigen (PSA) to double, known as the PSA doubling time (PSADT). The faster PSA levels double in the blood, the greater the risk for developing distant metastases, and the more urgent it is for them to receive treatment.[12]

Currently, three ARis are used to treat patients with nmCRPC. Enzalutamide and apalutamide have very similar molecular structures. Darolutamide, on the other hand, has a unique structure that increases its flexibility, and confers higher polarity and more hydrogen-bond-forming potential.[13-17] Its structure could be the reason for its limited potential for drug-drug interactions (DDI), an important factor when managing comorbidities in patients with prostate cancer.[18-20] The unique structure of darolutamide could also explain the drug's low blood-brain barrier penetration in rodent models compared with other ARis.[13-17,21] This finding was further supported in a study on healthy volunteers, in which darolutamide caused similar changes to placebo in regional cerebral blood flow.[22] This could lead to a low potential for central nervous system-related adverse events in patients.[15-17,21,22]

The three ARis have been studied in three placebo-controlled Phase III trials.[18,23,24] The ARAMIS trial (NCT02200614),[25] sponsored by Bayer, studied the efficacy and safety of darolutamide in males with high-risk nmCRPC.[19,26]

Figure 1: Prostate cancer disease progression.[1-5]



ADT: androgen deprivation therapy; M0: cancer has not spread to other parts of the body; M1: cancer has spread to other parts of the body; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; nmHSPC: non-metastatic hormone-sensitive pancreatic cancer.

The PROSPER trial (NCT02003924),[27] sponsored by Pfizer, studied enzalutamide, and the SPARTAN trial (NCT01946204),[28] sponsored by Aragon Pharmaceuticals, Inc., studied apalutamide.[29,30] Each trial enrolled around 1,500 patients with nmCRPC with short PSA doubling times, equal to or less than 10 months.

Compared with placebo, all three ARis demonstrated significantly extended OS, reduced risk of dying (darolutamide by 31%; enzalutamide by 27%; apalutamide by 22%), and longer median times to metastasis.[18,19,23,24,26,29,30]

"Of course, those endpoints are not the only thing important for patients," explained Bögemann. Softer targets, like time to cytotoxic chemotherapy or antineoplastic therapy, were also significantly improved with the three ARis.[19,29,30]

Importantly, patients treated with darolutamide showed a robust PSA response, which can help to reduce the PSA-related anxiety that affects many males with prostate cancer.[31]

To test drug tolerability, researchers consider drug discontinuation rates, incidences of adverse events, and deterioration of QoL. Darolutamide fared well overall, with a discontinuation rate close to that of placebo (8.9% versus 8.7%, respectively). It also had a very low incidence rate of side effects. For example, fatigue was reported in 33% and 46% of patients who were drug-treated in the SPARTAN and PROSPER trials, respectively, but in only 13% of patients treated with darolutamide in the ARAMIS trial.[18,19,29,30] Patients treated with darolutamide reported a significant delay in deteriorating QoL scores compared with placebo.[18,19,30] QoL was also maintained in patients who received enzalutamide in the PROSPER trial and apalutamide in the SPARTAN trial.[29,30]

Bögemann concluded that darolutamide can be used to extend the OS of nmCRPC patients with very good tolerability, helping to maintain QoL and alleviate PSA-related anxiety. "I think using darolutamide is very useful for the nmCRPC patients that we treat," he added.

Metastatic Hormone-Sensitive Prostate Cancer: Does Early Treatment Intensification Improve Survival and Delay Progression to Metastatic Castration-Resistant Prostate Cancer?

Bertrand Tombal

mHSPC is prostate cancer that has metastasised but remains susceptible to treatment with ADT. It can be discovered at initial presentation of prostate cancer, or develop from recurring locoregional nmHSPC. Most males with metastases progress to mCRPC within a median of 1 year.[5] Treatment guidelines have been modified for patients with mHSPC over the years, following the results of several clinical trials.

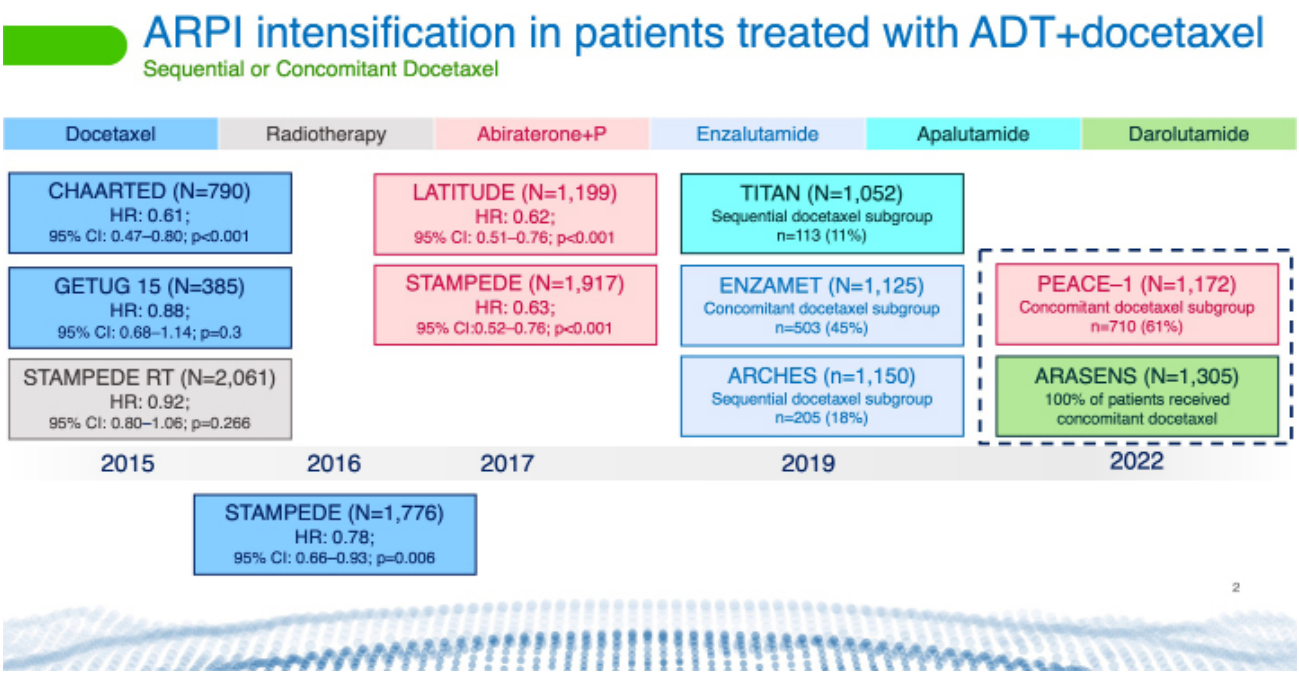
For years, said Tombal, hormone therapy and sometimes surgical castration were the only available options for treating patients with newly-diagnosed metastatic disease. Everything changed with the publication of the GETUG-AFU15 (NCT00104715)[32] and CHAARTED (NCT00309985)[33] trials (Figure 2), he said.[34,35]

These trials, which ran from 2004–2008 and 2006–2012, respectively, assessed the efficacy and tolerability of ADT with or without docetaxel. This regimen was tested in males with de novo metastatic disease, known as synchronous metastases, and in males whose metastases developed following treatment of localised prostate cancer, called metachronous metastases. Both studies reported improvement in progression-free survival with ADT plus docetaxel compared with ADT alone. However, the GETUG-AFU15 trial did not find a significant difference between the two approaches in OS.

"So, for a few months, we lived with some uncertainty," said Tombal. "And many times when it's like this, you need a third trial to adjudicate."

This is what the STAMPEDE trial (NCT00268476)[42] provided (Figure 2).[36] This trial, which has been ongoing since 2005, showed that adding docetaxel to ADT significantly increased OS in patients with mHSPC.

Figure 2: Timeline showing Phase III clinical trials using different therapies.[5,34-41]



ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibition; CI: confidence interval; HR: hazard ratio; P: prednisone.

"If you ask me, 15 years down the line, what was the benefit of docetaxel?" said Tombal, "I would say that, beyond increasing OS, it was a tipping point for multidisciplinary management of prostate cancer. For the first time, urologists had to sit down with medical oncologists to discuss the best treatment for patients."

The results also changed treatment guidelines. Clinicians were advised to give ADT in combination with chemotherapy to every patient presenting with stage M1 disease. "We have learned a lot since then," added Tombal.

For example, a meta-analysis by the STOPCAP M1 collaboration of individual participant data from the CHAARTED,[33] GETUG-AFU15,[32] and STAMPEDE[42] trials found that docetaxel appeared to improve progression-free and OS for all males with mHSPC, except those with low-volume, metachronous disease.[43]

The same study did show, however, that there was some benefit to giving docetaxel to patients with low- and high-volume stage T4 lesions. "But clearly, when it comes to docetaxel, volume and timing matters," said Tombal.

Things changed once again for mHSPC treatment with the arrival of ARPIs. Currently, these are the three ARis, apalutamide, enzalutamide, and darolutamide, in addition to abiraterone acetate. "Within 5 years, we had confirmation from five trials (Figure 2) that adding an ARPI to ADT very significantly increased OS [versus ADT alone], notwithstanding volume and timing of metastases," said Tombal.[5,37-39,41,44]

Current European Association of Urology (EAU) guidelines now recognise this. The guidelines recommend offering ADT in combination with docetaxel if first presentation is M1 and the patient is fit for treatment with the chemotherapeutic.[45] ADT and abiraterone acetate plus prednisone, or apalutamide, or enzalutamide, are recommended for patients whose first presentation is M1 disease, and who are fit for that regimen.[45] ADT and radiotherapy should be offered when first presentation is low-volume M1 disease.[45] "[The guidelines] have not been reviewed yet for darolutamide, explaining why it is not there," said Tombal. This may change with emerging evidence.

Now, two clinical trials, PEACE-1 (NCT01957436)[46] and ARASENS (NCT02799602)[47] (Figure 2), are investigating the effects of treating patients with mHSPC with a combination of ADT, docetaxel, and an ARPI.[48,49]

"When we designed the [ARASENS][47] trial with Bayer in 2014–2015, the question we asked was: if a patient requires ADT plus docetaxel, is there room to add one ARPI? For us, from the start, darolutamide was an optimal agent, because it had very little drug-drug interaction [...] and was extremely well tolerated. We also knew from 22 trials in CRPC that docetaxel was a very difficult bride to be married," because combining drugs with docetaxel often increases its toxicity.

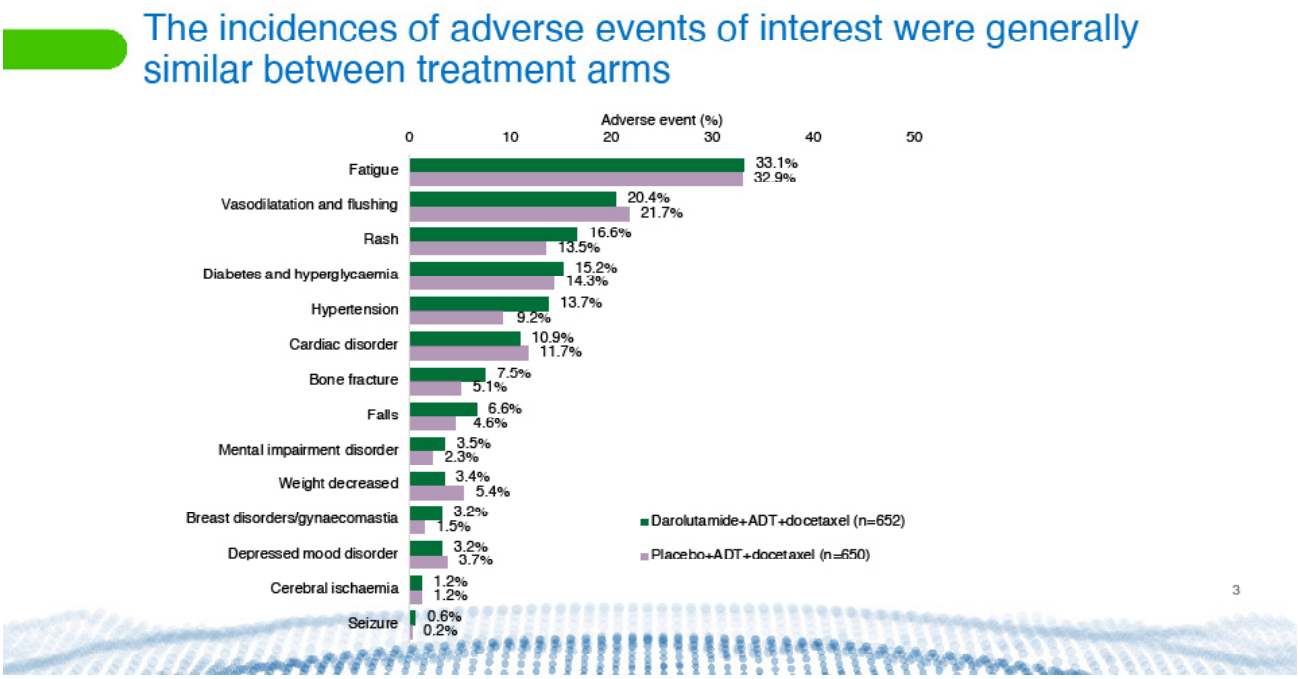
The ARASENS[47] trial, which evaluated concomitant ADT, docetaxel, and darolutamide in 1,305 patients with mHSPC, found a significant improvement in OS, with a 32.5% reduction in the risk of death compared to ADT and docetaxel alone.[50] "Keep in mind that these were probably high-volume, high-risk patients with aggressive disease because they were selected [to receive] docetaxel," said Tombal.

The trial found that addition of darolutamide did not affect patients' ability to complete six full cycles of docetaxel, nor did it increase the incidence of adverse events or drug discontinuation due to treatment-emergent adverse events (Figure 3).[50] Importantly, docetaxel toxicity did not increase.[49] Docetaxel doses have to be reduced in some concurrent trials with other ARPIs to make it tolerable, said Tombal. "This is not the case here."

Currently, discussions are ongoing about which patients should receive the triple therapy of ADT, docetaxel, and darolutamide.

Tombal and his colleague, Nicholas James, Professor of Clinical Oncology, Institute of Cancer and Genomic Sciences, University of Birmingham, UK, surveyed more than 70 participants at the Advanced Prostate Cancer Consensus Conference (APCCC) in 2021 about their preferred treatment options for the management of newly-diagnosed mHSPC. The survey found that 40% of participants recommend treating synchronous, high-volume mHSPC with the triple therapy of ADT plus docetaxel and ARPI.[51]

Figure 3: Comparison from the ARASENS47 trial of incidences of adverse events of interest between patients with mHSPC who received darolutamide plus ADT and docetaxel or placebo plus ADT and docetaxel.[50]



ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer.

The question then remains: which of the ARPIs should be used in combination treatment of mHSPC? Comparing them can be tricky, explained Tombal, as different drug trials have used different patient populations and measured side effects differently. "So you have to be extra careful."

A simple metric to look for, in this case, is the proportion of patients who discontinue treatment due to adverse events. The ARASENS[47] trial showed a percentage difference of 3.0% between patients with mHSPC who discontinued combination treatment of darolutamide, ADT, and docetaxel compared with the arm given ADT, docetaxel, and a placebo.[50] On the other hand, in the PEACE-1 trial, there was a 16% difference between the two arms of those treated with ADT and docetaxel plus with abiraterone and prednisone or ADT and docetaxel plus a placebo.[48]

"Abiraterone is a little bit more complicated to use compared with the other ARPIs apalutamide, enzalutamide, and darolutamide," said Tombal. This is because patients treated with abiraterone need frequent monitoring for side effects and DDIs.[52] This is especially important for patients with prostate cancer receiving treatments for comorbidities, which can often be the case.[53,20]

The take-home messages, said Tombal, are that docetaxel, abiraterone, and enzalutamide were first established as the standard of care for patients with mCRPC. The EAU guidelines then moved to recommend immediate intensification of ADT with an ARPI for treating patients with mHSPC.[45] Additional intensification with docetaxel should be discussed, said Tombal. Importantly, the DDI profile of darolutamide differs from that of other ARPIs, which is relevant to patients who are polymedicated. Finally, a favourable toxicity profile, convenient management, and different DDI profiles should be considerations in the treatment of patients with prostate cancer, concluded Tombal.

Case Studies in Non-metastatic Castration-Resistant Prostate Cancer and Metastatic Hormone-Sensitive Prostate Cancer: Translating Data to Practice

Christian Gratzke

"We all share the same treatment goals for males with nmCRPC and mHSPC," began Gratzke. "We all would like to extend survival and delay progression [from localised prostate cancer] to mCRPC. We would like to minimise adverse events [...] and also preserve long-term quality of life. I think quality of life preservation has now become a major issue. Patient-reported outcomes are more and more important, and I think are a key criterion for judging the success of a certain drug."

Gratzke described two case studies from his professional practice to illustrate how clinicians approach the treatment of different patients with prostate cancer.

A 44-Year-Old Patient with Metastatic Hormone-Sensitive Prostate Cancer

In July 2020, the PSA level of an asymptomatic 44-year-old male, whose father was recently diagnosed with prostate cancer, was found to be surprisingly high (18.2 ng/mL). They were given a 3-day course of antibiotics to rule out infection, and the test was repeated a month later. However, the PSA level had increased to 19.0 ng/mL. Imaging and biopsies suggested high suspicion for malignancy and metastasis.

Following discussions with a multidisciplinary team, the patient opted for a radical prostatectomy with extended lymphadenectomy in August 2020. Histology results from the resected tissue confirmed the previous findings. Eight weeks after surgery, the patient's PSA level had dropped from 19.00 to 0.71 ng/mL. Further imaging suggested a malignant lymph node in the right side of the iliac fossa. The patient was started on ADT and radiotherapy to the prostate bed and affected lymph nodes. The PSA level fell to 0.04 ng/mL, but rose again 2 months later in April 2021 to 0.06 ng/mL. By August 2021, the PSA level had reached 0.22 ng/mL.

The patient opted for a salvage lymphadenectomy to remove the malignant lymph node, but their PSA level rose to 0.24 ng/mL 2 months later.

Subsequent imaging and biopsy in March 2022 revealed new onset of liver metastases. The patient was placed on ADT, docetaxel, and darolutamide according to the ARASENS[47] protocol and, as of June 2022, has completed three full cycles. The patient has lost their hair and developed lymphoedema in the left leg, with thrombosis ruled out, but is otherwise doing well. The patient is determined to complete all six cycles of the triple therapy with the expectation of a good QoL once they are off chemotherapy, and is receiving only ADT and darolutamide.

A 68-Year-Old Patient with Non-metastatic Castration-Resistant Prostate Cancer

A 68-year-old male with no family history of cancer, and who had PSA levels within normal range for 10 years during regular checkups, suddenly presented with a PSA level of 6.55 ng/mL. The patient was given a diagnosis of high-risk, locally advanced prostate cancer following imaging and biopsy. They also had previously diagnosed non-valvular atrial fibrillation and hyperlipidaemia, and were receiving medication for these conditions.

Histology results following a radical prostatectomy and lymphadenectomy confirmed prostate cancer Grade T3a, International Society of Urological Pathology (ISUP) 4, with negative margins, and no positive lymph nodes.

The patient recovered well but, 2 years later, in March 2017, their PSA level rose to 0.25 ng/mL, so they received radiotherapy and ADT. By May 2017, the patient's PSA levels had dropped to 0 ng/mL.

In December 2018, the patient's PSA level had risen again above 2 ng/mL and their testosterone fell significantly to reach castrate levels. Their PSADT was around 2 months, and a CT scan was negative for metastases but positive for local recurrence, including in small lymph nodes in the pelvis.

Following proactive discussions of the options with oncologists, the patient was given darolutamide according to the ARAMIS[25] protocol. Scans carried out 16 weeks later showed that the pelvic lesions were progressively shrinking and no new lesions were apparent. The patient continues to do well on darolutamide and is experiencing only minor fatigue. They are waiting for their next imaging follow-up.

Discussion

Imaging and the Treatment of Non-metastatic Castration-Resistant Prostate Cancer

Tombal began the panel discussion by asking about the role of modern imaging in treatment decisions for patients with nmCRPC.

Gratzke and Bögemann agreed that a negative prostate-specific membrane antigen (PSMA) PET scan is not a reason to delay ARi treatment in a patient with nmCRPC who is in "good shape," but shows a PSADT of 7 months.

"Why would you wait if you had a drug that is able to prolong survival and metastasis-free survival with a good quality of life?" said Gratzke. "There is no real, good argument to do so."

A PSADT of 7 months means there is a high risk of developing metastasis within a short period of time, added Bögemann. So, even if the PSMA PET scan is negative, why wait, he agreed.

Tombal provided another example of a patient who had undergone prostatectomy and radiotherapy following rapid progression. Initially, their PSMA PET scan was negative and so ARi treatment was deferred. However, 3 months later, their PSA had doubled and a subsequent PSMA PET scan showed a large metastasis on the hip. The patient's doctors opted for radiation therapy only. Tombal asked if the panel agreed with this approach.

When there is systemic disease, there is a very good rationale for offering systemic treatment, Gatzke responded. Radiation is still important, however, especially if the patient is experiencing pain or has a risk of fracture.

However, Gatzke explained that another patient described by Tombal with a very slow PSADT of 1 year and a PSMA PET scan with two defined bony metastases would be considered low risk. In this case, radiation therapy would be used to treat the metastases, with frequent imaging to monitor the response. In contrast to the previous patient with a very short PSADT, it is acceptable to delay systemic treatment in this low-risk case until imaging shows further progression, Gatzke said.

Triple Treatment Options for Metastatic Hormone-Sensitive Prostate Cancer

The panel then discussed options for triple therapy treatment of patients with mHSPC. High-volume mHSPC patients are considered good candidates for this approach, whereas low-volume, recurrent patients are not. The choice of ARPI to use within the triple therapy regimen should be guided by currently available evidence, which points, said Bögemann, towards darolutamide and abiraterone. Gratzke added: "Even if this was not an industry-sponsored symposium, I would not know why I wouldn't be prescribing darolutamide in that aspect."

Is There a Rationale for Genetic Workups Before Treatment?

Panellists answered this question from the floor, with Tombal explaining that current guidelines advise genetic workup in patients with a family history of cancer, with newly-diagnosed metastatic cancer, and in patients with intraductal and cribriform prostate cancer.

Patients with newly-diagnosed metastatic cancer found to have certain genetic mutations could qualify for treatment with a class of drugs called poly (ADP-ribose) polymerase inhibitors that cause cell death. Otherwise, genetic workups are more for the purposes of genetic counselling, and have broader implications for research, explained Tombal.

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3D Printed Models Decentralise Surgical Skills Training for Retrograde Intrarenal Surgery and Percutaneous Nephrolithotomy in the COVID-19 Era

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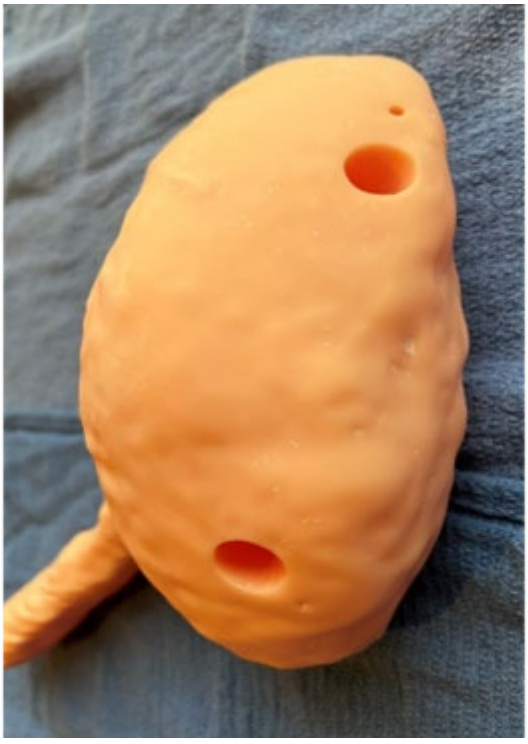
BACKGROUND AND AIMS

Imparting the required psychomotor skills for trainees to become proficient in percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS) is tricky for surgical educators due to the challenging nature of the procedures and the lack of realistic simulators. The current COVID-19 pandemic has compounded these issues by reducing learning opportunities for trainees through reduced case numbers and the availability of surgical skills courses. To address these contemporaneous

Figure 1: The 3D printed retrograde intrarenal surgery and percutaneous nephrolithotomy trainer.



issues, the authors have developed 3D printed inexpensive combined RIRS and PCNL training models for both in-person and video conference skills training.

MATERIALS AND METHODS

Anonymised CT data was used to develop the training model, using medical image processing software (3D Slicer version 4.12 [Surgical Planning Lab, Harvard Medical School, Harvard University, Boston, Massachusetts, USA]). The model was 3D printed using flesh-coloured resin, which best approximated the appearance of the collecting system during ureteroscopy. The face validity of the simulator was assessed by surgical educators for its suitability for both in-person and remote training.

RESULTS

The RIRS and PCNL training model was evaluated by expert urologists involved in the national training of the procedures and found to be more realistic and affordable when compared with available alternatives. The 3D printed model was developed for under 3 EUR, allowing multiple identical copies to be 3D printed for both in-person courses and scheduled video conferencing workshops, with the models distributed to each participating centre beforehand. This hub and spoke method of surgical skills training is greatly facilitated by the affordability of the 3D printed models.

CONCLUSION

The authors have developed an inexpensive combined RIRS and PCNL training model for both in-person and remote training at the Urological Society of Australia and New Zealand (USANZ) and other international training courses. 3D printed simulators have great future potential in the training of endourological and other urological procedures, enhancing connectivity and facilitating the decentralisation of training courses for the acquisition of key surgical skills. ●

Abstract Highlights

The following highlights cover several innovative and thought-provoking abstracts from the 37th European Association of Urology (EAU) featuring topics such as intravesical treatment in non-muscle invasive bladder cancer, artificial intelligence in recurrent urinary tract infections, and genetic risk in benign prostatic hyperplasia.

Different Responses To Intravesical Treatment In Non-Muscle Invasive Bladder Cancer Subtypes

RESEARCHERS have identified a clinical tool for enhanced identification of high-risk patients with non-muscle invasive bladder cancer (NMIBC) at high risk of progression, in a study presented at the European Association of Urology (EAU) in Amsterdam, the Netherlands between 1st–4th July 2022. Currently, the proposed treatment for high-risk NMIBC is intravesical Bacillus Calmette-Guérin (BCG) therapy; however, only one-half of patients with NMIBC benefit from this therapy. The risk classification is centred on the characteristics of the clinicopathology, and the understanding of molecular characteristics of BCG treatment failures is low. The study, using transcriptome analysis, was aimed at enhancing the risk stratification in patients with NMIBC, and determining the molecular association with treatment failure.

A uropathologist reviewed the tumours of patients in the study with primary high-risk NMIBC who had undergone BCG therapy. The patients were divided into two cohorts. Cohort A included n=132 patients with BGC-naïve tumours (n=69 non-responders versus n=63 responders), and n=44 patients after BCG therapy relapse. RNA from the tumour tissues was isolated, containing over 80% of cancer cells, and was used for RNA-sequencing. Progression-free survival was the primary endpoint and a consensus clustering was utilised to establish the molecular subtypes. In order to further explore the subtypes linked to progression-free survival, the researchers performed differential expression, pathway, immune deconvolution, and regulon analyses. The results were verified using an independent cohort B group that included n=151 patients with BCG-naïve tumours. The results from the RNA-sequencing data showed that there were BCG response subtypes (BRS): BRS1–BRS3. The patients with BRS3 tumours had a lower progression-free survival rate compared to patients with BRS1 or BRS2. The association of the BRS subtypes and progression-free survival rate was verified by cohort B group. This study demonstrated an improvement in the identification of high-risk patients with NMIBC at high risk of progression of the disease, and could be used to develop new therapies for specific subtypes in the future. ●

"The study, using transcriptome analysis, was aimed at enhancing the risk stratification in patients with NMIBC, and determining the molecular association with treatment failure."

Could Artificial Intelligence Guide Antibiotic Choice in Recurrent Urinary Tract Infections?

IN CURRENT practice, the management of patients with recurrent urinary tract infections (rUTI) is difficult, particularly as the natural history of the infection is not completely understood. Artificial intelligence (AI), which is providing promise in many areas across the healthcare sector, could be used to guide antimicrobial choice in cases of rUTIs.

Researchers carried out a study across Urology departments at three different sites: the Santa Chiara Regional Hospital, Trento, Italy; the University of Trieste, Italy; and Oslo University Hospital, Norway. Investigators aimed to define a neural network that has the ability to predict both the clinical and microbiological efficacy of antimicrobial treatment, and which could be used as standard in the clinical practice setting. They included records from a large cohort of 1,043 females affected by rUTI between January 2012–December 2020. All of these patients had undergone antimicrobial treatment for their uncomplicated lower urinary tract infections.

Microbiological and clinical data was collected from both the initial appointment and the first follow-up consultation after the symptomatic episode. Researchers included all available data regarding the previous use of both antibiotics and antibiograms. Data were analysed using NeuralWorks Predict (NeuralWorks Technologies, Pune, Maharashtra, India) software, and were compared with univariate and multivariate analysis results.

Following several initial stages of running AI learning and prediction processes, researchers concluded that the use of artificial neural networks in females with recurrent cystitis had a sensitivity of 87.8%, and a specificity rate of 97.3% when predicting the clinical and microbiological benefits of the prescribed antimicrobial drug during the follow-up consultation.

Both AI and statistical analyses discovered that previous use of fluoroquinolones (hazard ratio [HR]: 4.23; p=0.008) and cephalosporins (HR: 2.81; p=0.003) in the last 3 months, along with the presence of cotrimoxazole-resistant *Escherichia coli* (HR: 3.54; p=0.001), were the most influential variables which affected the output decision when predicting fluoroquinolone-based therapy failure.

Tommaso Cai, Santa Chiara Regional Hospital, believes that the study was able to demonstrate both the reliability and feasibility of using AI applications in guiding antimicrobial choice in patients with rUTIs. With its effectiveness in predicting both performance and outcomes, it is hoped that AI could also help to achieve antimicrobial stewardship principles. ●

"Investigators aimed to define a neural network which has the ability to predict both the clinical and microbiological efficacy of antimicrobial treatment, and which could be used as standard in the clinical practice setting."

Analysis of Treatment Persistence Rates in Female Patients with Overactive Bladder

REAL-WORLD data analysing treatment persistence in females commenced on therapy for overactive bladder (OAB) has revealed that 1-year treatment persistence rates are lower than previously reported.

A retrospective cohort study presented at the 37th Annual EAU Congress in Amsterdam, the Netherlands, on 3rd July 2022, by Karin Lifshitz, Department of Urology, Tel Aviv Medical Centre, Israel, showed that rates of 1-year treatment persistence dropped progressively throughout the year, and were lower than previous reports suggested.

The study included 46,079 females who had been commenced on either anticholinergic or β3–adrenoreceptor agonist treatment for OAB between 2010 and 2020, with the aim of understanding true treatment persistence rates in this patient cohort. Patients were classified as not persisting with treatment if they had not refilled a prescription for 90 days. Advanced data-mining techniques were used to obtain information from the largest regional provider's medication purchase database for all females who had commenced OAB medication over the 10-year time period.

The findings from this study showed that overall treatment persistence progressively reduced from 49% at 30 days to 9% at 1 year. Persistence rates were highest with mirabegron (β3–adrenoreceptor agonist) and oxybutynin (anticholinergic) at 10% and 11%, respectively. This is lower than the persistence rates of 40% for β3–adrenoreceptor agonists and 25% for anticholinergics reported in previous studies. Persistence rates for all other medications in this study was 4%. The authors also identified that those who persisted with treatment were older than those who did not persist with treatment by 5.3 years.

"The findings from this study showed that overall treatment persistence progressively reduced from 49% at 30 days to 9% at one year."

Whilst OAB therapeutics have proven efficacy, rates of overall 1-year treatment persistence in this study were low, at 9%. Further research to elucidate the underlying reasons behind this could be performed in order to improve management and treatment pathways for patients with OAB. ●

Genetic Risk in Benign Prostatic Hyperplasia

GENES are driving the pathophysiology of benign prostatic hyperplasia (BPH), according to Richard J. Bryant from the Nuffield Department of Surgical Sciences, University of Oxford, UK, who presented data on a large, genome-wide study at EAU22.

BPH is a common condition in males who are middle-aged and older, and causes significant morbidity. Despite this, there is an unmet need to identify the condition's genomic drivers that lead to surgery. The identification of new pharmacological interventions is also important, as current treatments only consist of a few agents.

Bryant and colleagues conducted a study of BPH by using information from three databanks: 126,082 subjects from the UK Biobank; 44,093 from the Japanese biobank RIKEN; and 756,878 from 23andMe. This came to 110,916 cases of BPH and 816,137 controls.

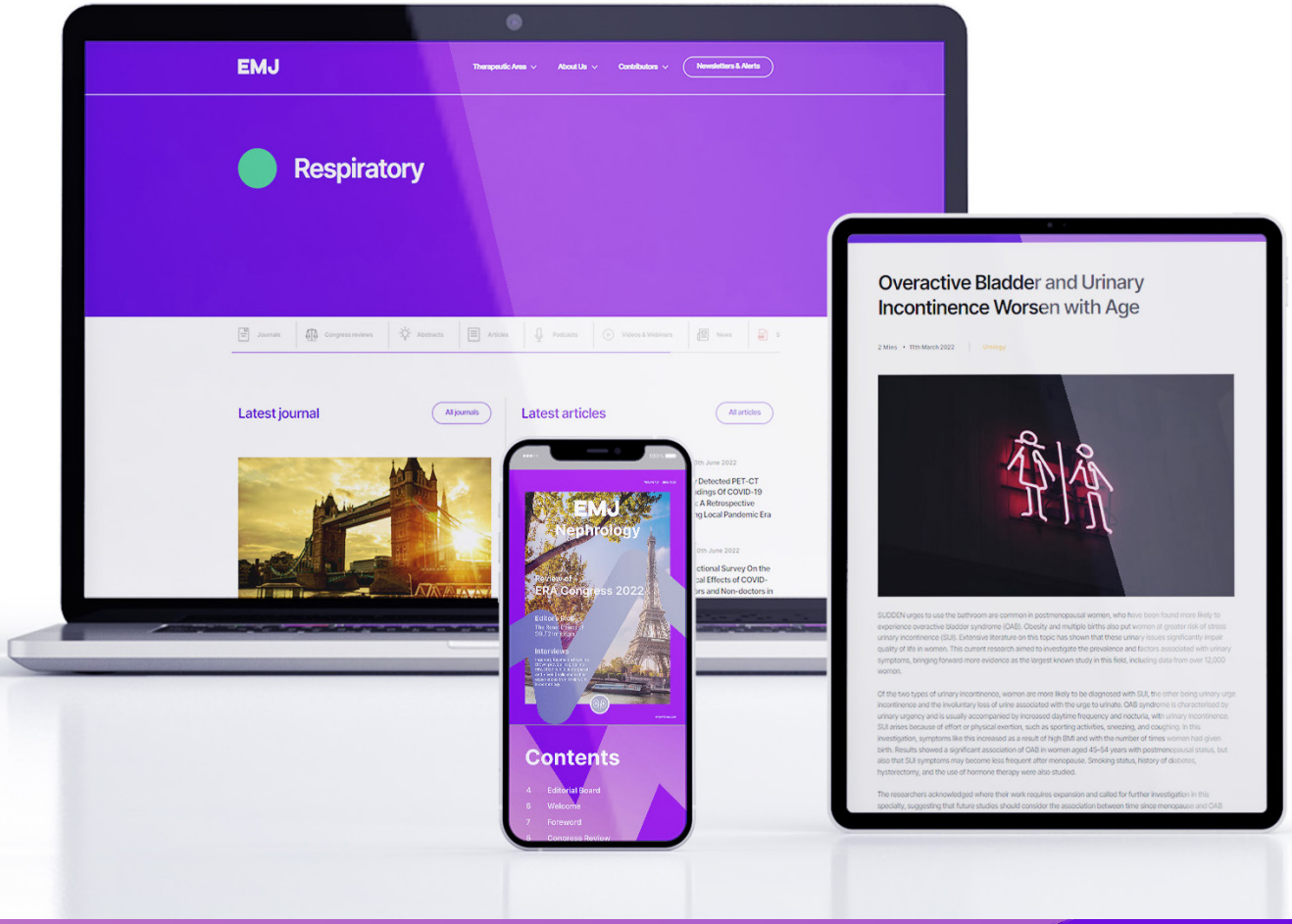
Creating a BPH genetic risk score, the researchers were able to assess the prognostication of specific genes. They also investigated selected genes using differential expression between single cell subtypes in BPH samples and those from a normal prostate.

The researchers discovered a total of 17 loci were associated with BPH, and only two of them were associated with males with Western European and Japanese origin, suggesting ethnicity-specific risk alleles. This study also illustrated that associated genes had differential expression in cells that derived from BPH compared with normal prostate, and demonstrated how the *NKX3.1* homeobox gene plays a role in BPH in basal epithelial cells.

"The researchers discovered a total of 17 loci were associated with BPH, and only two of them were associated with males with Western European and Japanese origin, suggesting ethnicity-specific risk alleles."

Some genes in this analysis are tractable to drug-repurposing or therapeutic targeting, representing new targets for development and treatment. This is important for males with BPH who were treated surgically, as they had a higher genetic risk score than those who were not surgically treated.

Revealing potential candidates for future therapeutic development, this study indicates that genetic risk scores correlate with BPH severity and the need for surgical treatment. Understanding the importance that genes play in the pathophysiology of BPH is a step towards personalised medicine.



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EMJ Interview

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Q1 Was there a defining moment or set of moments that led you to choose a career in urology and specifically prostate cancer (PCa) surgery?

When I was a House Officer after finishing medical school, the first job I did was in urology. I had never considered urology beforehand and had not been exposed to it much through medical school. When I did that urology job, I remember meeting the consultants and thinking that this was actually very nice. I remember going to some of their houses and they all had nice sports cars and houses, and I thought this is a job with a good lifestyle.

Following this, I went to London and worked for Lord Bernard Ribeiro, who became the first Black President of the Royal College of Surgeons (RCS). I worked for him, and he was a true General Surgeon. He worked in general surgery, and also did thyroids and urology. When I worked for him, I really enjoyed the urology aspect of the role, so that pushed me into urology.

In terms of PCa, when I was a Junior Trainee, one of my programme directors took a liking to me and sorted me out with a fellowship in New York, USA, for a few years with a very famous PCa surgeon to learn robotic PCa surgery from him.

Q2 Your personal education and professional experience have involved you travelling to numerous destinations such as the USA and Germany. Where do you believe you gained the most experience, and do you believe travelling was integral for you to make it to where you are today?

Yes, it was certainly the case. I believe you always learn more when you learn from different people and different systems. So, even if you work with great people here, there is more to learn elsewhere as well. There's more than one way of skinning a cat and there's more than one way of doing something, and there's more than one good way of doing something.

It's very useful, no matter how good your training is locally, to expand your horizons, see different perspectives, and actually going and working with the best in the world. New York, Sweden, Oxford, and London, etc., it all adds to that mix of who you are as a doctor, as a urology surgeon, as a PCa surgeon. Therefore, it was a really helpful experience because it gave me different perspectives and different ways of doing things. I always learn something from different people

who are all experts in their field. It's not like it's a competitive thing; it is in fact a collegial thing.

In terms of bang for my buck, I believe the place where I gained the best experience was in New York, USA, because I went on fellowship there for 18 months. On most days, I pretty much worked from 6 a.m.–8 p.m. While there, I published 36 papers in 18 months, presented over 50 times at international meetings in 18 months, and had 11 months in surgery. I did what would have been quite a few years' worth of training condensed into a very short period of time because of the level of intensity. It was where I trained with one of the world leaders in my field of PCa, and is probably where I learnt the most in the shortest period of time.

Q3 You currently have two published books, over 20 book chapters, and 10 newspaper articles to your name for your research in PCa and robotic surgery. What do you believe to be the current gaps in literature and what topics merit greater attention?

One of the things that I'm very much interested in is the value of surgery and robotic surgery, in particular in males who are suffering from more advanced disease. We have demonstrated, through a lot of the work that I and others across the world have done, the value of robotic surgery for localised PCa, curing cancer, or the long-term control of cancer, and also in reducing side effects. We have optimised surgery for localised PCa; however, what we haven't been able to do yet is to identify males who have life-threatening disease, beyond localised disease, and who may benefit from a cure and actually increase their life expectancy for a disease that would otherwise be considered incurable. We now need to move from just optimising outcomes in the population with localised PCa, and move on to these advanced cases. Currently, we are looking to see how we can actually improve cure rates and long-term cancer control rates in males who are diagnosed with advanced disease, and trying to stop it from then progressing onto very advanced, life-threatening disease. We need to get to that bridge of actually expanding our surgical indication or treatment indications to capture males who need it more because they are more likely succumb to their disease.

Q4 You have contributed greatly to the field of urology. Could you share any exciting findings or current research going on in your department?

I have two or three different affiliations, but my main NHS clinical affiliation is at University College London Hospitals (UCLH), UK. We've just received a grant for our hospital through The Urology Foundation (TUF) Innovation and Research Fund to run a study looking at males who are highly likely to be incontinent after robotic prostatectomy. We are running a study where we compare conventional robotic surgery with a new type of robotic surgery called Retzius-sparing robotic-assisted surgery, which is only performed by a few expert surgeons across the entire country. I'm one of those surgeons and, therefore, in a good position to run such a study. We're looking to see if males who are likely to be incontinent after standard robotic surgery can do better with this newer form of robotic surgery. This is an innovative study, and we're hopefully going to start this study soon at UCLH.

I also work privately at Cleveland Clinic London, UK, where I'm the Lead for urology. There, we are hopefully going to set up other studies that are mostly going to look at patient-reported outcome measures, so that we are able to assess how males recover after surgery from our perspective as doctors, and also ask patients directly. What you find actually is, when you look at patient reported outcomes, they often vary considerably compared to what doctors

think. For example, if a doctor asks if you are incontinent, you're far less likely to say “Yes” than when filling out an evaluation, because of an underlying desire to please the doctor, an attitude that many patients have. In order to truly see how patients are reacting and responding to the interventions given to them, it's important to carry out patient reported outcomes. We're investing a lot of time and effort in trying to get those embedded within all patients who present with PCa and other urological diseases that have outcomes that require management.

Q5 Advanced PCa is one of the most common urological diseases. Have you seen much improvement in its treatment over the last few years?

Advanced PCa, which is not contained and has already spread outside the prostate, beyond the lymph nodes, and perhaps into the bones or other places, is typically considered incurable; however, now we have newer systemic drugs beyond hormone treatment or standard hormone treatment, such as abiraterone, and chemotherapeutic agents that have already been shown to improve survival from this population. At present, a male who is diagnosed with metastatic or advanced PCa is likely to do a lot better than they would have done a few years ago.

On top of that, my interest is looking to see whether curative modalities such as surgery can also further improve survival rates in these patients. That is where I think there's still some work to be done. That is where we are focusing our efforts: to try and improve survival rates of these affected males.

Q6 Are there any innovations on the horizon in the field of urological surgery that you think are particularly noteworthy?

One of the great things about urology surgery is that there are always lots

of innovations, because it's a very technical specialty with a lot of gadgets. Although it's a surgical specialty, there's not a huge amount of open surgery anymore; however, there are a lot of robotics, and endoscopic surgery with telescopes. It's endoluminal, endoscopic surgery, or robotic surgery, and there are new robots and tools. These are bigger and better tools with smaller footprints, more versatility, and better vision. Additionally, better dexterity platforms are emerging that will help to improve the outcomes for patients, which, at the end of the day, is what it's all about. It's a bit like a PlayStation 1. We thought it was great but now we have the PlayStation 5, and PlayStation 1 seems outdated. It's the same way with urological surgery. It is much more advanced now, with instrumentation and robotic devices that we can use which, of course, have improved outcomes for our patients.

Q7 You currently are in the research panel of TUF. Can you talk about the ways in which TUF aims to empower patients and create a dialogue aimed at optimal healthcare benefits?

TUF is a very nice charity. I've been involved with this organisation for many years, even before I was appointed to the research panel; now, I'm involved in the assessment of research proposals from different colleagues to see which ones are worth funding. Back in the day, even before I became a PCa surgeon, they helped fund me to go on some visits to the USA, from Florida to New York, to see what PCa surgery and robotic surgery was all about. They inspired me to go off and learn that technique, so they've been very instrumental in supporting urologists like me. They funded my research and a trial that I've just finished, which has been recently been published.

Additionally, they have funded a study of the new surgical technique that I mentioned earlier: Retzius-sparing robotic-assisted surgery. The way in which they support urology patients is by supporting urology doctors and by funding these doctors to do patient-related research. If you look at all of my research, it's all patient-focused research. It's not about sitting in a lab with test tubes of DNA. Instead, it's been patient-focused, looking into patient outcomes and at various techniques and surgical modalities, and then comparing them to see what's best for the patient. TUF is very good at that kind of research and getting great buy-in from patients to participate, and also to propagate the findings of that research to patients.

"The way in which they support urology patients is by supporting urology doctors and by funding these doctors to do patient-related research."

Q8 As a committee member of the UK National Cancer Research Institute (NCRI) Advanced Prostate Clinical Studies Group, could you please explain what this position entails, and how it contributes to the success of the association and patients' healthcare?

The NCRI has various groups; PCa is one, and there is an advanced PCa subgroup. It is a government research structure. So, for example, if you decide you want to do research in PCa, you need to have approval after peer review process from some form of governance such as the NCRI in order for you to get funding from a large funding body.

People who want to do research in advanced PCa present their idea to the NCRI advanced PCa subgroup. We will look at all those proposals, critique them, and provide feedback, so that

when they then apply for funding, they have the best proposal to try with. Additionally, the funders know that it's been through us, a peer review group of experts who have looked at this proposal and approved it. It's a way of being engaged with the PCa community, to see what researchers and other experts in the UK are doing, being able to provide input into that and, therefore, being able to create a high-quality research agenda for the country.

We are also interested in understanding what patients want, as there's no point in patients joining research studies that are not likely to succeed, or are of no use. If we're going to ask patients to go the extra mile and take part in a study, which may not necessarily affect them directly but will help others like them, then we need to make sure it's the best quality research. Being able to participate in that governance structure to ensure that we have high-quality research coming through is very rewarding for me.

Q9 Are there any innovations on the horizon in the field of urological surgery that you think are particularly noteworthy?

There are new robotic manufacturers out there. Intuitive (Sunnyvale, California, USA) dominated the market for 20 or more years. It was the same way when I was growing up, when BT (London, UK) was the only telephone provider. Now, of course, we can get phones from hundreds of different providers. In the same way, there are lots and lots of different robotic manufacturers coming into the market, and that raises the bar for everybody. When you have a monopoly in any field there's no reason for innovation and progress, but as soon as that monopoly is broken and new people come in, the quality goes up and cost goes down. That benefits patients in the long run. I think that having more competition in the market is creating greater versatility of robotic procedures and at a lower cost, which also benefits patients.

Q10 Finally, what advice would you give to young healthcare professionals pursuing a career in this discipline? Where do you hope they will take the field of urology and, specifically, robotic surgery and PCa research and developments over the coming decades?

The future is bright for urology because we have so much innovation, with new robots and technologies coming into the market. I would tell them to stick with urology and pursue it, as it provides you a great mixture of medicine, minimally invasive surgery, and robotic and endoscopic surgery, and it has a huge variety for them.

In terms of research, a lot of it is urology surgery but also diagnostic urology, which has a lot to do with cancer work. A quarter of all cancers across the board are urological cancers, with PCa being the most common cancer for males in the Western world. There's a huge potential to improve the field of cancer and do cancer research, while still working as a practising urologist. One could do basic science, cancer research, clinical cancer research, and clinical operating work as well, so there's so much variety in the field.

I believe the field of robotics will continue to get better, just as it has in robotics outside of urology. The same way we can put the Mars Rover on the moon, we'll be able to have better surgical robots for enhanced surgical procedures, and even more precise procedures. That's a huge benefit for urologists but also the research side in terms of cancer biology, and trying to find better treatments and better cures for cancer which, again, is hugely exciting. Hopefully I will see that in my career over the next 10–20 years.

The Debate on Prostate Cancer Screening: What Does the Wisdom from the Old Books Whisper?

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Abstract

Prostate cancer is a prevalent problem in male healthcare. The previous decades have witnessed some significant improvements in the knowledge of aetiology and pathology, as well as practice of screening, treatment, and follow-up of the disease. A downstaging at the time of the diagnosis and increase in the survival were vivid with the advancements, albeit the screening of the disease using regular prostate specific antigen measurements was previously debated. In this paper, the authors aimed to inform the reader on the course of the prostate cancer along a century by sailing along the chapters of the old urology textbooks.

INTRODUCTION

Textbooks are the cornerstone of education. In conjunction with civilised society and the initiation of modern printing techniques, they have become a kind of joint monument of humankind, manifesting the era in which the books were written.[1] From the perspective of prostate cancer investigators, the authors would first like to provide the reader with an additional point of view on the effects of the modern approach to treating prostate cancer, by tracing the course of the disease through textbooks from different decades, and then discussing the place of the prostate-specific antigen (PSA)-focused prostate cancer screening on ageing males' healthcare.

As one will clearly realise from the referred narratives, prostate cancer was a major concern in the healthcare of an ageing male, which is quite akin to today's world, while even archaeological evidence suggests that the disease has always been a valid problem that might have been the culprit of mortality.[2,3]

COURSE OF PROSTATE CANCER DIAGNOSIS, TREATMENT, AND PROGNOSIS OVER DECADES

History has witnessed some merges in the practice of handling an individual with a prostate cancer diagnosis. The variance is not only evident for the treatment modalities; the paradigms of the diagnostic approach have also evolved over time.[4,5]

Harry C. Rolnick's two-volume textbook, *The Practice of Urology*, had its roots in Rolnick and Daniel N. Eisendrath's collaborative reference book *Urology*, which was initially published in 1928.[6] The company made further publications of the book in 1930, 1934, and 1938.[7-9] When *The Practice of Urology* was published in 1949, it praised Huggins' research on the effect of hormones on the prostate and significant amount of phosphatase enzymes in the gland.[10] They classified malignancy into three distinguished types, namely the inflammatory, disseminating, and scirrhous types, which are entirely irrelevant to the current classification. The clinical presentation was defined as having dramatic symptoms, while the diagnosis was recounted to be based on surgical removal of the organ after a suspicious prostate examination per rectum. Serum acid phosphatase measurements, which further evolved into PSA measurements, were proposed to have both diagnostic and prognostic value. Yet the author conceded that the diagnosis was often too late to undertake surgery, which was the only curative method during the era.[10]

Meredith F. Campbell had created a legacy in urology with his comprehensive work titled *Urology*, first published in 1954.[11] After his death in 1969, the tradition continued with the name *Campbell's Urology* until the 9th edition. The bible of urology was kept alive in the name of *Campbell-Walsh Urology* in the 9th–11th editions, while the contemporary edition honours the names of Campbell, Walsh, and Wein.

The 2nd edition of *Urology* by Campbell has a well-sourced chapter for 'Carcinoma of the prostate', authored by William W. Scott, and William N. Toole.[12] The authors cited prostate cancer as the third-leading cause of cancer mortality, with an uncertain aetiology, and a diagnosis solely based on a rectal examination. Biopsy amenities were also restricted; thus, a surgical biopsy was prevalent. They further reported that their journey with operable prostate cancers started with 5.1% in 1949, and the rates rose to 19.0% in 1958 by careful and widely performed prostate examinations and biopsies. They concluded that a 5% rate of operability within the USA was a reasonable figure. Hypophysectomy and adrenalectomy, which seem ridiculous today, were discussed in the text, along with periprostatic radioactive gold injections and endocrine therapy. As a corollary to the diagnosis of the disease in its late phase and insufficient treatment stances, the authors summarised the chapter by citing prostate cancer as a common disease with an unknown aetiology, and often a lethal result.[8]

On the other side of the Atlantic, John Blandy announced his book, *Urology*, which was published by Blackwell Scientific Publications in the UK in 1976. Blandy co-authored the 'Carcinoma of the prostate' chapter with Kenneth E.D. Shuttleworth.[13] They came around with the previous authors on the late presentation of the disease that is characterised by either the symptoms of urinary outflow obstruction or metastases. They described rectally positioned hand-guided transperineal or transrectal true-cut prostate biopsy techniques, as well as radical retropubic prostatectomy. Interestingly, they illustrated a bladder wall tubularisation procedure to overcome post-prostatectomy incontinence, and they proposed a pelvic exenteration procedure in the treatment of prostate cancer in the name of super radical prostatectomy.

Even the awareness of the disease seems to affect the course of the disease onward two decades between Rolnick's *Urology* to Blandy's *Urology*.[14] The Blandy text debates the situation of early-diagnosed prostate cancer, which is thought to be a matter of active surveillance or radical treatment, as well as some cases that may not necessitate any intervention during their natural lifespan, which is considered for watchful waiting in contemporary practice.[13]

DISCOVERY, ANNOUNCEMENT, USAGE, AND CONTROVERSIES OF THE PROSTATE-SPECIFIC ANTIGEN

Arguably, the most prevalent discovery affecting the clinical approach to an either a patient or a healthy senior who admitted for regular screening, is a type of protein that is most widely known as PSA. This protein was heralded by independent researchers in slightly different steps of the discovery. At least nine prominent scientists were involved in the distinguishing, description, and purification of the molecule during a 20-year period between 1960 and 1980.[14] However, even the labour of the molecule has some controversies.[15]

Despite its non-specific nature, PSA was swiftly engaged in the urologists' armamentarium and become a valuable tool in the diagnosis, risk-grouping, observational management, as well as the post-treatment follow-up of a patient who has or is a candidate for having prostate cancer. Furthermore, PSA measurements were initiated to being obtained from asymptomatic seniors, and the practice found itself a place as a population screening tool. The screening was either offered or discouraged from time to time by public health institutions or urological associations due to the available evidence.[16]

The contemporary clinical guideline of the European Association of Urology (EAU) endorses offering a risk-adaptive screening approach focused on the risk groups and life expectancies, while the American Urological Association (AUA) also underlines the importance of a screening strategy, weighing the risks and benefits as well as using a shared decision-making approach. Both associations are compatible with each other's conception on avoiding PSA screening in subgroups who may get more harm than benefit from the treatment, and will probably get no benefit from an active treatment modality in his natural lifespan.[17,18]

The National Comprehensive Cancer Network (NCCN) is also in favour of practicing an early diagnosis strategy for well-informed individuals who are in risk groups and/or would benefit from the early diagnosis.[19] On the other hand, the United States Preventive Services Task Force (USPSTF) made an official statement against routine PSA screening in 2008 and 2012, which was revised to make a decision considering possible benefits, and building an informed decision-making strategy for small groups in 2017. The final decision of the USPSTF in 2018 still underlines the potential of a small benefit, which is not always prevalent, and which may bring harm together.[20]

CONTEMPORARY EVIDENCE AND DEBATE ON THE PROSTATE CANCER SCREENING USING PROSTATE-SPECIFIC ANTIGEN IN ASYMPTOMATIC SENIORS

There is a high level of evidence on the benefits, or the possible harm, of PSA-based prostate cancer screening. For the attention of the reader: the discussion and the debate are on the role of PSA-based prostate cancer screening on a population level, though it should not be confessed with the role of PSA measurements in symptomatic individuals.

Bartsch et al.[20] pioneered the field of prostate screening studies with their valuable work in Tyrol, Austria. Their study compared the mortality rates and oncological stages between Tyrol, a federal state with a newly-implemented PSA screening programme, with the rest of the country in which there was no kind of screening offered during the study period. Their non-randomised study started in 1993, and the results were announced in 2001. They reported a nationwide reduction in mortality as well as a downstaging of the disease. Moreover, the reduction and the stage migration in Tyrol was reported to be better respective to the rest of Austria during this study period. Further updates of this study are also published, and it is reported that an ongoing reduction of mortality was relevant in this studies' population even after 10 years of follow-up.[21,22]

The initial randomised evidence is made available by Labrie et al.[23] with their 11-year long study. The Quebec study randomised more than 46,000 males to either screening (over 30,000 males) or non-screening (the remaining population). Overall, they reported more than a 60% reduction in prostate cancer-specific mortality, which was quite spectacular, and criticised in the subsequent papers.[24]

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial can be clearly considered as a milestone, considering its extensive targets, in both prostate cancer research and the field of medical oncology. This study randomised more than 75,000 males in screening and non-screening arms with very close number of individuals in both groups. With a high compliance to the screening which is a little over 80% and 10 years of follow-up, the researchers reported similar prostate cancer mortality rates in both groups.[25] Unfortunately, despite its well-planned initiation, the data of the PLCO study is reported to be missing some essential requirements to draw a reliable decision of the screening.[26]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) study can be considered as the most undistorted data with the highest level of evidence we have in contemporary literature.[27] Participant groups also published the district data from participant countries of the ERSPC, which is quite valuable in evaluating the patterns of screening and the clinical results in different European countries.[28-30]

Furthermore, 13 and 16 years of follow-up data from the ERSPC was also published.[31,32] This study successfully enrolled and followed up more than 180,000 males from seven countries, and the ERSPC data showed a substantial reduction in prostate cancer specific mortality at 9, 12, and 16 years of follow-up. The benefit is far more remarkable in some participant countries, namely Sweden, for instance.[30]

The USA data also approved the findings of the ERSPC. Howrey et al.[33] made a retrospective analysis of data from 1,067 counties and reported that 61 deaths were prevented between 1998 and 2006 for every 100,000 males receiving a PSA test in 1997. The same PSA test number resulted in 1,597 males undergoing prostate cancer treatment during the same period. Thus, they concluded that the PSA-based prostate cancer screening resulted in a notable increase in prostate cancer diagnosis and treatment. However, the overall reduction mortality was modest at best, and they pointed out the risk of overtreatment and overdiagnosis in exchange for the modest reduction in mortality.

FROM HISTORY TO TODAY: WHERE are we NOW?

Since the late 1980s, PSA has been used in the diagnosis of prostate diseases, either benign or malign. This test was approved by the U.S. Food and Drug Administration (FDA) in 1994 and is widely adopted by urologists in their daily practice. Since then, extensive usage of PSA levels in evaluation of healthy senior males started to affect the course of the disease. As mentioned above, the disease has long been a leading cause of mortality with low chance of surgical cure.

About three decades after the approval of PSA for use in the routine clinical practice by FDA, the last edition of the urologic bible, *Campbell Walsh Wein Urology*, comprehensively discusses the aetiology and pathology of prostate cancer with a special emphasis on providing a management strategy to patients without leading to any harm.[34] It is now argued that more diagnoses are made or are made earlier than needed, causing damage for the sake of treating the cancer or leading to the stress of individuals because of continual screenings. All this confirms that what has been done in the clinical evaluation of prostate cancer has commutated a lethal monster to a domestic beastie.

Of course, all of the achievements cannot be attributed solely to PSA screening. During this period, oncological care, surgical care and approaches, preventive measures in the healthcare systems and, overall, technology and life quality have all improved. However, the authors still think that this screening is the leading factor during the presented timeline that changed the practice of care for patients with prostate cancer. In the light of their journey through the urological texts, the authors again propose that the prostate screening collaborating with PSA measurements should continue, while the research on the management of the disease and application of the screening to different populations should also continue to serve the best practice we can provide to patients. vendaecto quibus et et erem velia ne nonsece aquostium cusciet invent excerci ratur, adit doluptatem is qui doluptur, utesed quiaectatur mo molendam, aut dolo od qui invenis si aut voluptatetur alit velent.

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BLADDER CANCER

RISK FACTORS

- Smoking
- Exposure to certain industrial chemicals and past radiation exposure
- Chronic bladder inflammation
- Genetic mutations linked to bladder cancer
- Treatments for certain diseases

DETECTION

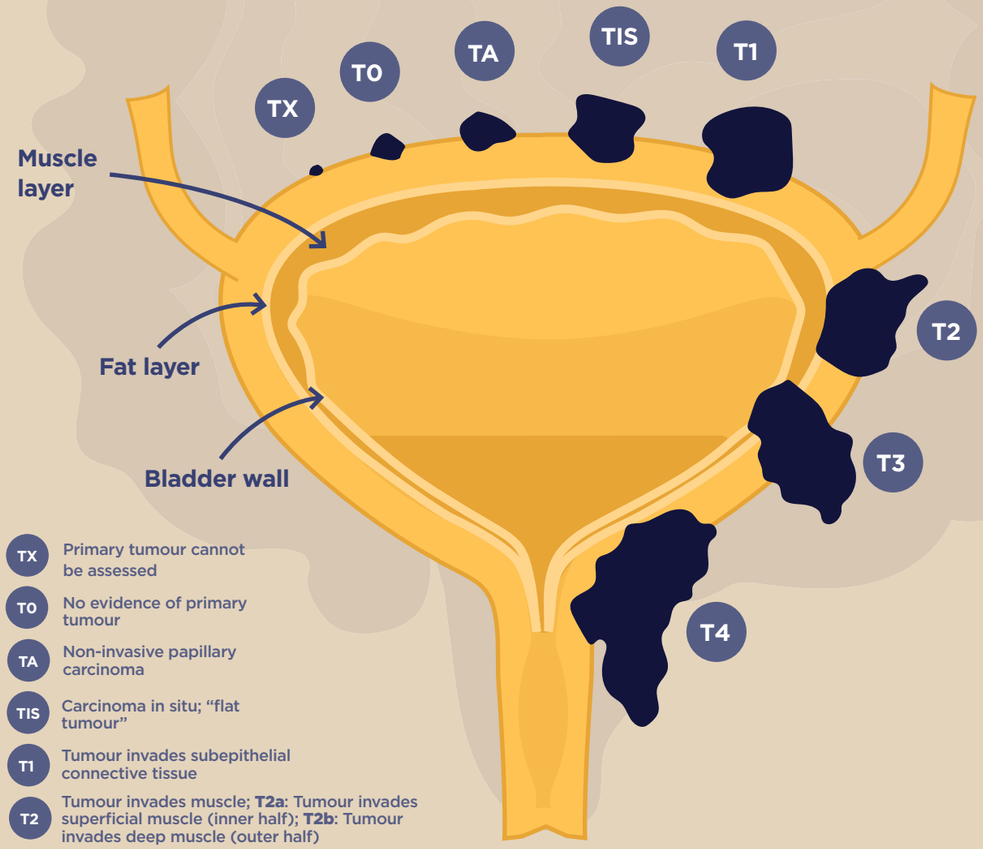
- Cystoscopy
- MRI
- CT urogram
- Ultrasound

TREATMENT OPTIONS

Transurethral resection (TUR) for muscle/ non-muscle invasive bladder cancer → **Tumour staged (TNM system) & subsequent treatment based on tumour stage**

- **Repeat TUR**
- **Partial/total cystectomy**
- **Intravesical immunotherapy/ chemotherapy**
- **Radical surgery +/- bladder reconstruction**
- **Systemic chemotherapy / immunotherapy**
- **External beam radiation therapy with TUR and systemic chemotherapy**

TUMOUR STAGES



- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **TA** Non-invasive papillary carcinoma
- **TIS** Carcinoma in situ; “flat tumour”
- **T1** Tumour invades subepithelial connective tissue
- **T2** Tumour invades muscle; **T2a**: Tumour invades superficial muscle (inner half); **T2b**: Tumour invades deep muscle (outer half)
- **T3** Tumour invades perivesical tissue; **T3a**: Microscopically; **T3b**: Macroscopically (extravesical mass)
- **T4** Tumour invades adjacent organs. **T4a**: Tumour invades prostate stroma, seminal vesicles, uterus, or vagina; and **T4b**: Tumour invades pelvic wall or abdominal wall

EPIDEMIOLOGY

Smoking accounts for approximately

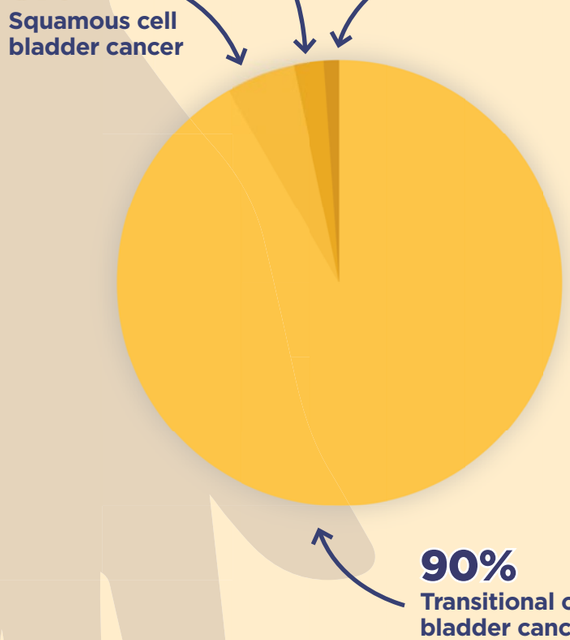
50-65% of new cases each year

Males are **five times** more likely to be diagnosed with bladder cancer than females

90% of diagnoses are made in those **over the age of 55**

The **5-year survival rate** for bladder cancer in the USA is **77%**

TYPES OF BLADDER CANCER



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Primary Penile Squamous Cell Carcinoma in a Patient with Metastatic Adenocarcinoma of Colon to Liver: A Case Report

Editor's Pick

In this issue of *EMJ Urology*, the article 'Primary Penile Squamous Cell Carcinoma in a Patient with Metastatic Adenocarcinoma of Colon to Liver: A Case Report' by Son et al. outlines a novel case of a patient presenting with two separate tumours that are unrelated genetically: penile squamous cell carcinoma and colorectal adenocarcinoma from the colon to the liver. Penile cancer is rare, representing only 1% of all malignancies in males, and squamous cell carcinoma accounts for the majority of penile cancers. Although it is not unusual to see metastatic disease at the time of presentation of penile squamous cell carcinoma, this is a rare occurrence, and co-presentation with penile squamous cell carcinoma has not been established in literature.

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Abstract

Penile squamous cell carcinoma (SCC) is a rare malignancy associated with human papillomavirus and immunosuppression. If not detected early in its course, local invasion and metastasis to distant regions often occurs. Colorectal adenocarcinoma (CRAC) is the third most common malignancy worldwide. Many familial genetic mutations are associated with CRAC; however, co-presentation with penile SCC has not been established in literature. The authors present a case in which a patient presenting with a primary diagnosis of penile SCC was found to have distant liver metastases due to a previously unknown recurrence of CRAC. The authors conclude

that primary penile cancer with subsequent metastatic colon adenocarcinoma is possible in patients with unknown genetic predisposition.

Key Points

1. Penile squamous cell carcinoma (SCC) is a rare malignancy, presenting in 1% of males, and is associated with human papillomavirus and immunosuppression.

2. Many familial genetic mutations are associated with colorectal adenocarcinoma (CRAC), but co-presentation with penile SCC has not been established in literature; this case report outlines a case of concurrent primary penile SCC with a recurrence of CRAC.

3. Genetic mutations that interrupt tumour suppressor genes or mismatch repair pathways could account for a co-presentation of another primary malignancy alongside CRAC.

INTRODUCTION

Penile cancer is rare, representing only 1% of all malignancies in men. Squamous cell carcinoma (SCC) accounts for over 95% of penile cancers.[1] Closely-related conditions include Bowen's disease and Erythroplasia of Queyrat, both of which tend to progress to invasive disease, whereas bowenoid papulosis does not have malignant potential.[2] Risk factors for penile SCC include uncircumcised males, human papillomavirus (HPV), immunosuppression, chronic infection, phimosis, poor hygiene, multiple sexual partners, and tobacco exposure.[2,3] Diagnosis is delayed in up to 50% of patients due to fear, carelessness, and embarrassment.[1,4] This delay often leads to detection of advanced disease, as one-third of patients have progressed beyond organ-confined disease at the time of diagnosis.[4] The most common site of metastasis of penile SCC is regional superficial inguinal lymph nodes and then sequentially the deep inguinal and pelvic lymph nodes before visceral spread.[1] The staging of SCC based on lymph node involvement is a studied predictor of survivability, with inguinal lymph nodes having approximately 80% survival rates, while pelvic lymph nodes have 0–33%.[5] Primary presentation of distant metastasis of penile SCC is rare and occurs late in the course of the disease.[4]

Colorectal adenocarcinoma (CRAC) is the third most commonly diagnosed cancer worldwide, accounting for 10% of annual cancer diagnoses, excluding skin cancers.[6] Risk factors include adenomatous polyps, family history, age, tobacco use, alcohol use, and processed meat intake. Inherited conditions such as familial adenomatous polyposis and Lynch syndrome increase likelihood of a CRAC diagnosis.[6] In this case, the authors present a patient without known genetic risk factors diagnosed with primary penile SCC with concurrent metastatic CRAC to the liver.

CASE DESCRIPTION

A 65-year-old male with a past medical history of Type 2 diabetes, hypertension, dilated cardiomyopathy, colon cancer status post-sigmoid colon resection, and end-colostomy 6 years prior to presentation, presented to the emergency department with dizziness and weakness that had lasted for 1 week. The patient also reported penile tension for the past 18–24 months, with associated swelling and bleeding from a circumferential penile lesion. At the time of the patient's colostomy reversal, a penile lesion was noted, and the patient was referred to the urology department; however, this coincided with the start of COVID-19 pandemic, creating various barriers to follow-up for the patient.

A physical exam revealed skin pallor and a 9 cm erythematous, friable, bleeding circumferential penile mass. There were no palpable inguinal lymph nodes on the physical exam. The patient's haemoglobin was 5.2 g/dL, necessitating transfusion of two units of packed red blood cells. A CT with intravenous contrast of the abdomen and pelvis detected lymphadenopathy in the left inguinal region measuring up to 1.7

Figure 1:
A) Coronal sections of CT abdomen and pelvis showing multiple low attenuation lesions in the liver;
B) calcified lesion of liver;
C) enlarged right external iliac lymph nodes.

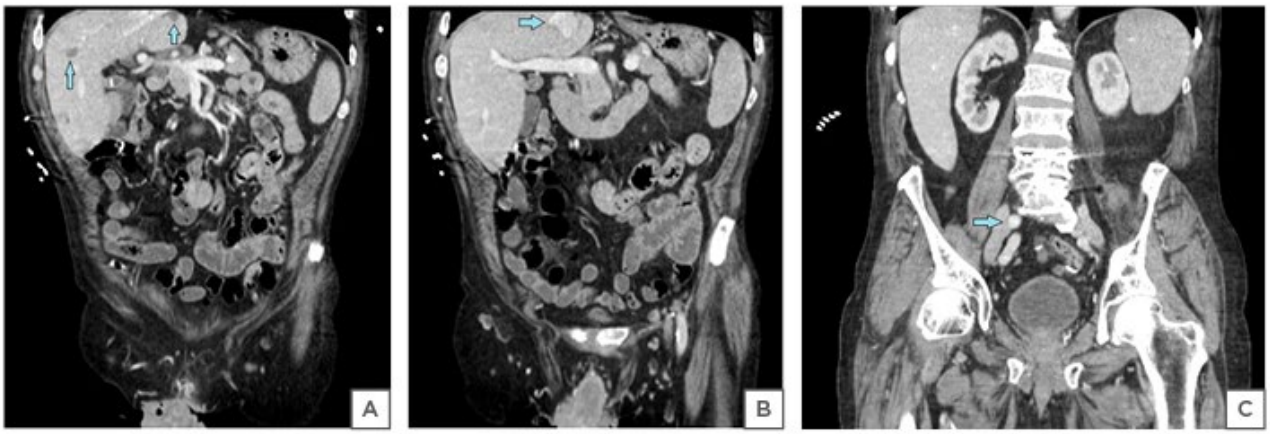
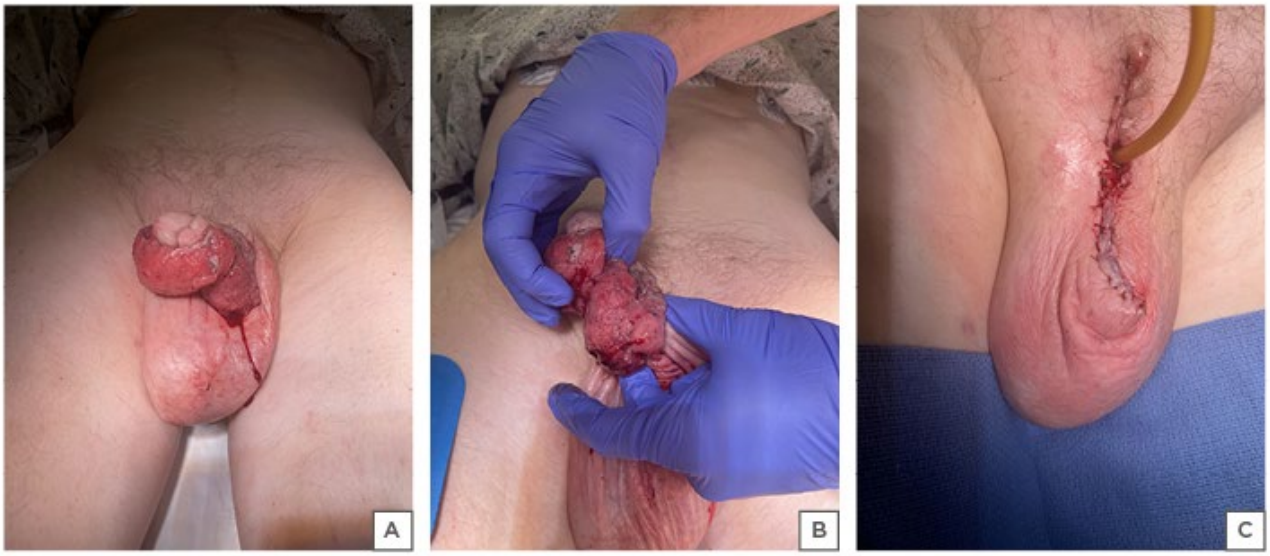


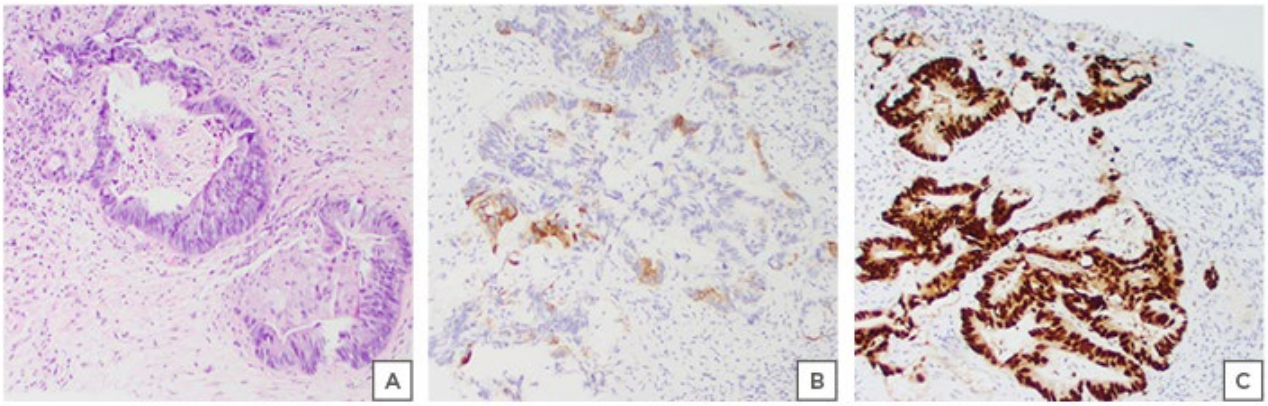
Figure 2: A, B) Circumferential penile mass before; and C) after partial penectomy.



cm, and the right external iliac region measuring 1.1 cm (Figure 1). There were multiple low attenuation foci scattered throughout the parenchyma of the hepatobiliary system. There was a 3.5 cm calcified lesion in the right middle lobe of the liver, as well as two additional 2.7 cm and 1.9 cm calcified lesions in the right posterior lobe and the right inferior lobe, respectively. Evaluation of the gastrointestinal tract was limited during this study given the absence of enteric contrast. The patient was admitted to the hospital for anaemia secondary to a bleeding penile mass.

During the hospital course, bleeding was noted from the ventral and dorsal aspects of the penile mass. Bedside interventions to control bleeding were attempted, including application of oxidised regenerated cellulose, pressure dressing with gauze, and silver nitrate; however, haemostasis

Figure 3: Interventional radiology liver biopsy consistent with A) adenocarcinoma; B) immunological stains positive for CK20; and C) CDX2.



could not be achieved. Due to the inability to control the bleeding, an additional five units of packed red blood cells were transfused.

A penile biopsy was unable to be performed due to the bleeding risk; therefore, palliative penectomy was elected. The pathologic specimen was an exophytic tumour measuring 9.1 cm x 8.5 cm x 3.8 cm with its papillary surface positive for p16 and p40 markers, confirming invasive, poorly differentiated SCC, classified as an HPV-related, basaloid-type penile intraepithelial neoplasia (Figure 2). Tumour extension was also noted into the scrotum, making the primary tumour Stage pT4. Negative margins of 2 cm were achieved with subsequent pathologic confirmation.

Interventional radiology-guided liver biopsy was performed on the first post-operative day, which revealed metastatic adenocarcinoma inconsistent with a primary source of penile SCC, and more characteristic of a primary tumour of colorectal origin. Immunological stains confirmed that the cells were positive for CDX2 and cytokeratin 20, both markers for metastatic CRAC. Stains were negative for cytokeratin 7 and p40, markers strongly associated with squamous epithelial origin carcinoma (Figure 3).

After a liver biopsy, the patient required no further blood transfusions and was discharged on the third post-operative day. In total, they were an inpatient for 13 days. A follow-up with medical oncology recommended an inguinal ultrasound to assess for lymphadenopathy. No palpable inguinal lymph nodes were appreciated during this office visit. Liver involvement from colon cancer was staged at advanced metastatic Stage 4. The disease was noted to be treatable, but not curable. The patient elected to undergo palliative chemotherapy and adjuvant radiation therapy for local control.

DISCUSSION

CRAC and SCC necessitate different treatment modalities and carry different prognoses. It is crucial to ascertain the origin of metastases, especially when dealing with the presence of uncertain metastases, as described in this case.[7] While penile SCC itself is rare, concomitant presentation with metastatic CRAC adds another layer of novelty. Initial patient presentation of a circumferential penile mass with hypodense liver lesions suggested the possibility of penile metastasis. Ideally, liver biopsies would have been obtained prior to surgical intervention to confirm malignancy and origin of metastasis. However, in the best interests of the patient, and as a necessary step to control bleeding, palliative penectomy was performed.

After the confirmation of metastatic CRAC to the liver, prophylactic inguinal lymph node biopsy was deferred in the patient. This region of the lymphatic system falls into a potential overlap for the spread of penile SCC and CRAC: penile SCC has predictable lymphatic drainage to the

deep inguinal, iliac, and pelvic lymph nodes prior to systemic spread.[8] Conversely, CRAC has the tendency to spread haematogenously to liver, lung, and brain,[5] but there has been reported literature of skip metastasis of CRAC to inguinal lymph nodes and external iliac lymph nodes.9 The decision not to perform lymph node biopsy leaves an unanswered question to this case: were pelvic lymph nodes enlarged due to spread of penile SCC, CRAC, or reactive? According to the National Comprehensive Cancer Network (NCCN) guidelines for penile cancer,[10] enlarged pelvic lymph nodes are recommended to be biopsied if feasible. If the lymph nodes are involved, chemoradiotherapy is recommended in patients who are non-surgical candidates.[10] In the setting of Stage 4 metastatic colon cancer, an interdisciplinary decision to start chemotherapy for metastatic disease superseded the inguinal lymph node biopsy.

Penile cancer is rare in the general population. Risk factors for penile cancer are HPV, lack of circumcision, and genetic mutations.[2] Histological evaluation of the penile specimen classified the sample as HPV-related basaloid intraepithelial neoplasia. HPV is a common, often asymptomatic infection, and it is a reasonable hypothesis that at some point, the patient may have acquired an undocumented HPV infection which predisposed them to later developing penile SCC.

In contrast to penile SCC, CRAC is a common malignancy that has both genetic and behavioural risk factors, including alcohol consumption.[11] The patient had ongoing alcohol abuse, with documented consumption of up to 28 standard drinks per week. While ethanol itself is not carcinogenic, once oxidised, its acetaldehyde intermediate can exert carcinogenic effects by binding DNA through deterring replication and mitosis, and can even serve as a photosensitiser upon binding DNA. While this is a known risk factor for CRAC, reports in literature also link alcohol intake with SCC risk.12 Also, recent evidence suggests that males who drink alcohol are 2.3 times more likely to develop inguinal lymph node metastases from penile cancer than those who do not (considered less than eight drinks per year).[13] The patient's high alcohol consumption, plus the ambiguity of return of the CRAC, may have contributed to an immunosuppressed state, leading to increased susceptibility for SCC.

A genetic aetiology for the two aggressive malignancies is another consideration that cannot be overlooked. Due to the frequency and aggressiveness of documented colonic polyps on a previous colonoscopy, as well as the patient's paternal history of CRAC diagnosis in his 60s, genetic screening of a colorectal cancer panel was performed. This panel tested for well-documented mutations associated with early-onset CRAC (*CDH1*), Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *EPCAM*), familial adenomatous polyposis (*APC*, *AXIN2*, *NTHL1*), *MSH3*-associated polyposis (*MSH3*), *MUTYH*-associated polyposis (*MUTYH*), juvenile polyposis syndrome (*SMAD4*, *PTEN*), Li-Fraumeni syndrome (*TP53*, *CHEK2*), hereditary mixed polyposis syndrome (*BMPR1A*, *GREM1*), polymerase proofreading-associated polyposis syndrome (*POLD1*, *POLE*), and Peutz–Jeghers syndrome (*STK11*). Many of these conditions have interruption of tumour suppressor genes or mismatch repair pathways, which could account for a co-presentation of another primary malignancy along with CRAC.

The patient was negative for mutations in all of the genes mentioned. While a genetic aetiology for this rare presentation would have been the answer to multiple malignancies in this patient, the absence of these mutations does not rule out a genetic cause. It is possible that the patient has an unknown mutation that has yet to be characterised. There may be complementary mutations, or additional environmental or epigenetic factors that could explain the aggressive CRAC and co-occurrence with penile SCC. Without targeted therapy options for germline mutations, treatment options with palliative chemotherapy without curative intent were pursued.

CONCLUSION

The authors conclude that concomitant penile cancer and metastatic colon cancer can occur in patients without significant risk factors. The patient in this study was circumcised and negative for well-described germline mutations. The aetiology of aggressive malignancy in this patient is unclear. While it is not uncommon to see metastatic disease at the time of presentation of penile SCC, it is a rare occurrence, and not previously reported in the literature when those metastases are found to be associated with a primary tumour other than that of the presenting penile cancer.

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Pigmentary Maculopathy in Interstitial Cystitis/ Bladder Pain Syndrome Treated with Oral Pentosan Polysulfate: A Review

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Abstract

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a rare and chronic bladder condition. Pentosan polysulfate sodium (PPS) is the only oral medication approved specifically for the management of IC/BPS. In 2018, Pearce et al. reported for the first time a unique pattern of ocular pigmentary maculopathy exclusively in IC/BPS patients following PPS exposure. This publication triggered several published studies, case reports, case series, and media reports claiming a link between PPS and pigmentary maculopathy; however, a clear interpretation of these data is still awaited and there are currently no prospective, well researched, confirmatory data available.

The clinical presentation of pigmentary maculopathy is characterised by moderate visual impairments and macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy. Most patients experiencing this ocular effect used high doses of PPS over an extended period, with risk of pigmentary maculopathy associated with PPS increasing with exposure. Studies that rule out prevalent retinal abnormalities are lacking. The cause of this particular maculopathy remains unclear and further research is required. The current data suggest that a median duration of 15 years of PPS exposure must elapse before

pigmentary maculopathy is detected. Furthermore, no increased incidence of any type of maculopathy is found up to a median duration of 5 years of PPS use. Thus, in line with the current European Medicines Agency (EMA) recommendation, if patients respond to therapy and a decision is made to continue PPS for longer than 6 months, a fundoscopy with optical coherence tomography (OCT) and fundus autofluorescence should be performed. In cases of no findings, the next eye examination should be after a further 5 years of PPS use; in cases of findings, continuation of the treatment should be re-evaluated by the urologist and monitored by yearly ocular fundus examinations.

This review provides a framework for evidence-based treatment with PPS in patients with IC/BPS using appropriate monitoring and gives an overview of the current understanding and evidence of the association of PPS and a specific pigmentary maculopathy.

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition of unknown aetiology. Symptoms can vary but there is typically pelvic pain or discomfort perceived to be related to the urinary bladder, usually accompanied by other urinary symptoms such as the persistent urge to void or frequency. Hunner's lesions and glomerulations (mucosal bleeding after bladder overdistension) are cystoscopic disease markers. Although a prevalence of up to 500/10,000 is reported for BPS, a substantially smaller prevalence of 1–5/10,000 is assumed for patients showing cystoscopic findings of glomerulations or Hunner's lesions corresponding to classes 2X to 3C type (European Association of Urology [EAU]/ESSIC classification[1] and National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] definition).[2]

PPS is indicated for the treatment of IC/BPS, characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency, and frequency of micturition. The recommended dose of PPS is 300 mg per day, taken as one 100 mg capsule orally three-times daily. It is the only oral medication specifically for the management of IC/BPS and was approved by the U.S. Food and Drug Administration (FDA) in 1996,[3] and subsequently by the EMA in 2017.[4]

In 2018, Pearce et al.[5] reported for the first time a unique pattern of ocular pigmentary maculopathy in IC/BPS patients following PPS exposure. Some patients who used the drug long-term for treating IC/BPS showed pigmented deposits that resembled little specks in the macula, associated with visual impairments. Publication of this small, retrospective case series triggered further articles discussing a possible link between PPS and pigmentary maculopathy.[6-13] These articles prompted an ongoing discussion in the media, and concern amongst patients with IC/BPS. As a result of the published findings, the summary of product characteristics[14] of PPS was updated in 2019[15] by the EMA and in 2020[16] by the FDA to include a pigmentary maculopathy warning with long-term use (>5 years), with recommendations for regular ophthalmological examinations.

This review article describes the ophthalmological features that distinguish this pigmentary maculopathy associated with PPS from other maculopathies and considers the evidence base for the nature of pigmentary maculopathy reported in patients with IC/BPS using PPS treatment.

INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME

IC/BPS is characterised by recurrent pain, pressure, and discomfort in the bladder and pelvic region that persists or recurs for more than 6 months in the absence of other identifiable causes.[17,18] In some patients with IC/BPS, the bladder is inflamed, ulcerated, scarred, or stiff. IC/BPS is often misdiagnosed as recurrent urinary tract infection, overactive bladder, or as prostatitis and benign prostatic hyperplasia in males.[19,20]

Pentosan Polysulfate Sodium (Elmiron)

In chemical terms, PPS is a semisynthetic sulfated polysaccharide, extracted from beechwood. Although the exact mechanism of action of PPS in the treatment of IC/BPS is not completely understood, the reported mode of action includes a local effect in the bladder where PPS binds to the deficient mucosa, protecting the urothelium from irritants and bacterial adherence to the cells.[14,21] The systemic anti-inflammatory activity of PPS supports the use of this drug to treat IC/BPS.[22,23]

Several randomised placebo-controlled studies[24-29] and meta-analyses[30-32] have shown that PPS is efficacious compared with placebo in the treatment of bladder pain, urinary urgency, and frequency of micturition in patients with IC/BPS. Its use is recommended by the guidelines of the relevant scientific societies in several countries, including EAU[33] and American Urological Association (AUA)[34] guidelines.

PPS is indicated for the treatment of IC/BPS associated with either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency, and frequency of micturition,[14] and is prescribed predominantly by urologists and gynaecologists.

PIGMENTARY MACULOPATHY IN PATIENTS WITH INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME

In general, maculopathy (or macular degeneration) is an ocular disease related to the central part of the retina called the macula, which is characterised by progressive loss of central vision and is irreversible in most cases. The main causes of maculopathy are age in age-related macular degeneration (AMD),[35] underlying disease like myopia, diabetes, secondary macular pucker and exudation,[36,37] genetics,[38] and drug intake.[39] Hereditary (genetic) maculopathy can be differentiated from acquired maculopathy.[40] An association between IC/BPS and retinal disease has not yet been reported.[5] From the patient's point of view, there are no differences in symptoms depending on the cause of maculopathy except for age of onset, which points towards genetic causes in younger patients.

In 2018, Pearce et al.[5] reported a unique pattern of ocular pigmentary maculopathy exclusively in six patients with IC/BPS following PPS exposure. The distinctive imaging features identified (see below) were subsequently reflected by Hanif et al.[41] and Christiansen et al.:[42]

1. Fundus photography revealing macular hyperpigmented spots, yellow-orange deposits, and/or patchy RPE atrophy;

2. Fundus autofluorescence imaging revealing a densely packed array of hyper- and hypoautofluorescent spots involving the posterior pole, centred on, and involving the fovea; and

3. OCT imaging, demonstrating focal thickening or elevation of the RPE with associated hyper-reflectance on near-infrared reflectance imaging.

This type of maculopathy resembles some aspects of AMD but, according to Christiansen et al.,[42] can be differentiated with the use of multimodal fundus imaging, and, according to Barnes et al.,[43] the same applies for a differentiation from hereditary maculopathies. In a cross-sectional study by Lyons et al.,[44] pigmentary maculopathy associated with PPS was accompanied by relevant visual function impairment that is not adequately identified by conventional visual acuity testing.

The potential mechanism of RPE damage by PPS is unknown. Whether PPS accumulates in the macular region or whether there is a mechanism comparable to the toxicity of chloroquine remains speculative.

In the following section, starting with the first report published by Pearce et al.,[5] subsequent reports are discussed including observational, cross-sectional, and case studies.

In 2018, Pearce et al.[5] reported the pattern of ocular pigmentary maculopathy in six patients with IC/BPS out of 38 patients with a diagnosis of IC/BPS and reported use of PPS on the electronic medical record system at the Emory Eye Center, Atlanta, Georgia, USA. The median age was 60 (range: 37–62) years, all patients received PPS with a median duration of exposure of 15.5 (12–20) years, and a median cumulative exposure of 2.26 (1.31–2.77) kg. Patients reported symptoms of difficulty reading and prolonged

dark adaptation without restrictions of central visual acuity and there were subtle funduscopic findings in these patients.[5]

In nearly all eyes, irregular vitelliform-like lesions were noted on funduscopic examination and OCT. Fundus autofluorescence imaging showed a well-delineated region in the posterior pole, with a highly irregular autofluorescence pattern characterised by hyperautofluorescent spots, surrounded by normal autofluorescence. The eyes of three patients had additional peripheral lesions, with a similarly irregular autofluorescence pattern, and the eyes of two patients showed patchy paracentral hypoautofluorescence, consistent with RPE atrophy. Near-infrared reflectance imaging revealed a similarly irregular reflectance pattern. OCT images from early stages demonstrated nodular excrescences at the level of the RPE and unaffected ellipsoid zones, but the clear separation between RPE/Bruch's membrane complex and the interdigitating zone was abolished. OCT in the areas of RPE defects showed loss of photoreceptors and the outer nuclear layer.[5]

In 2019, Hanif et al.[7] conducted another retrospective cross-sectional study to further evaluate the risk factors for development of the unique maculopathy among patients with IC/BPS. Eighty of 219 patients with IC/BPS in the study were on PPS and 14 showed all features of pigmentary maculopathy. The mean age was 61.3±12.2 years, the median duration of PPS intake and cumulative exposure were 18.3 (range: 3.0–21.9) years, and 2.30 (0.58–2.98) kg, respectively. There were no cases of unique maculopathy in the 139 unexposed patients and no other IC/BPS therapy showed a statistically significant association with this condition. Unfortunately, relevant demographic and anamnestic data were not provided.[7]

A further study by Hanif et al.[41] characterised the exposure and clinical manifestations of pigmentary maculopathy associated with PPS. This multi-institutional, retrospective case series included 35 patients. The median age was 60 (37–79) years, the duration of PPS intake was 15 (3–22) years, and the cumulative exposure was 1.61 (0.44–4.31) kg. Fundus examination of all eyes showed the clinical signs and imaging features of the macula outlined by Pierce et al.[5] and, in 24 eyes (36%), the lesions extended to the retinal periphery. Longitudinal evaluations in a few patients suggest dynamic changes in pigmentary abnormalities, according to Shah et al.[12]

In addition, a few single cases of potential maculopathies associated with PPS were reported in the form of case reports, but the facts presented were predominantly incomplete and unclear and not amenable to further evaluation.[45-47]

Two larger observational epidemiological studies have been conducted with respect to PPS and maculopathy in a broader context.

A retrospective, matched-cohort study was reported by Jain et al.[8] to assess a possible association between PPS use and macular disease. Defined outcome measures were any atypical maculopathy outcome and/or a diagnosis of AMD or drusen. A total of 3,012 users of PPS from a large national insurer's medical claims database in the USA were compared with 15,060 matched controls at 5 years, and 1,604 PPS users were compared with 8,017 matched controls at 7 years. Mean ages at the 5- and 7-years' time points were 52.3 and 52.8 years, respectively. At 5- and 7-years of follow-up, PPS use averaged only 10 and 13 months of prescription coverage, indicating either an incomplete database or sparse and irregular use of PPS by patients. In addition, no cumulative dose was identifiable.[8]

At the 5- and 7-year follow-up, there was no difference regarding the frequencies of atypical maculopathy. Regarding the diagnosis of AMD in addition to an atypical maculopathy, users of PPS showed no significant increase in odds ratio at 5 years ($p>0.130$), but a statistically significant increase at 7 years ($p=0.009$). Interestingly, sensitivity analyses including only patients with IC/BPS were reassuring an association for PPS and atypical maculopathy at 5 years, but not at 7 years nor in the atypical maculopathy+AMD analysis at 5 or 7 years.[8]

Ludwig et al.[13] reported a multicentre, retrospective cohort study of commercially insured patients in the MarketScan database (IBM, Endicott, New York, USA), which identified 49,899 patients with IC/BPS for whom

pharmaceutical data were available. Of those who filled a prescription for PPS (23%), the average patient filled a PPS prescription 125 days from their index IC/BPS diagnosis and filled prescriptions for 1,230 days of PPS in total.

A total of 1,335 (2.7%) patients with IC/BPS were diagnosed with maculopathy, most commonly exudative AMD (1.50%), drusen (0.80%), non-exudative AMD (0.30%), toxic maculopathy (0.10%), and hereditary dystrophy (0.04%). In unadjusted analyses, the percentage of patients who filled a PPS prescription and were subsequently diagnosed with maculopathy (2.37%) was very similar to the percentage of patients who did not fill a prescription (2.77%). Sensitivity analyses showed no significant increased risk of maculopathy following exposure to PPS. A dose-response relationship was not observed.[13]

Studies on Prevalence for a Pigmentary Maculopathy Associated with Pentosan Polysulfate Sodium

Data on prevalence are based on several prospective cohort studies

In a prospective university database cohort study by Wang et al.,[10] 741 patients on PPS were identified, of which 97 voluntarily participated in a prospective screening investigation. From among these 97 participants, 16 cases of pigmentary maculopathy associated with PPS were identified. Taking the ascertainment bias into account, a prevalence of 16.5% (16 out of 97) was cited by the study authors. Applying an intention-to-treat approach based on all exposed patients, which is common in prospective trials, showed a prevalence of 2.2% (16 out of 741). However, this might be an underestimate, as the number of patients with undetected maculopathy in the unexamined group of 644 is unknown. In an earlier interim evaluation of this study after the inclusion of 50 patients, Wang et al.[9] reported a prevalence of pigmentary maculopathy associated with PPS of 20% (10 out of 50). According to the data provided, only two of these 10 (4%) patients had pigmentary maculopathy, according to the definition given by Pearce et al.,[5] Hanif et al.,[41] and Christiansen et al.[42]

A recent retrospective chart review performed by Leung et al.[48] at a large retina-only practice showed that 33 (22%) of 148 patients with PPS exposure had signs of maculopathy. As none of these eyes fulfilled all the diagnostic criteria stipulated by Pearce et al.,[5] Hanif et al.,[41] and Christiansen et al.,[42] no further conclusions can be drawn. Moreover, genetic testing was performed in 16 out of these 33 patients and showed heterozygosity for variants of uncertain significance in 15. To note, the maculopathy group had a higher mean cumulative dose of PPS and longer duration of PPS use (1,600±849 g versus 864±852 g; $p<0.0001$; and 13.6 years versus 7.48 years; $p<0.0001$, respectively).[48]

Further indications on prevalence can be derived from the study by Ludwig et al.,[11] as described above. The percentage of patients who received PPS and were later diagnosed with maculopathy is estimated to be 2.4%. A similar prevalence of 2.0% (4 out of 216) was reported by Higgins et al.,[49] who conducted a chart review of a quaternary academic medical centre electronic medical record database. Kalbag et al.[50] described a prevalence of 1.5% (10 out of 131) based on electronic health record data.

Disease progression after cessation of pentosan polysulfate sodium usage

Retrospective data reported by Shah et al.[12] at the Emory Eye Center on 11 female patients with a total PPS exposure of 1.97 (1.55–2.18) kg, median treatment duration of 15 (3–22) years, and who were followed-up for at least 6 months after drug cessation showed that there was progression in the pattern of fundus autofluorescence changes and/or OCT findings in all eyes. No eyes exhibited a demonstrable improvement in disease after discontinuing PPS. A total of 7 eyes (32%) showed macular RPE atrophy at the baseline visit, and atrophy enlarged after discontinuation of PPS. In the absence of ongoing PPS exposure, the cause of progression of ocular disease cannot easily be explained.

Two additional case reports by Huckfeldt and Vavvas[51] and Barnett and Jain[52] each describe a potential case of pigmentary maculopathy associated with PPS, were inconclusive and the causality to PPS remains unclear.

DISCUSSION

The first report by Pearce et al.[5] of a unique maculopathy in patients with IC/BPS on PPS, more than 20 years after the launch of Elmiron (Janssen Pharmaceuticals, Beerse, Belgium), was a case series in a small number of patients in a single clinical centre, which was followed by several publications, predominantly from the Emory Eye Center[10] and other associated groups.[7,8,42,53]

Apart from several observational, cross-sectional, and case studies, there are two observational epidemiological studies,[8,13] which failed to identify a higher risk of maculopathy in patients with IC/BPS treated with PPS at 5 and 7 years. There are several inherent problems with these epidemiological studies. First, due to the broad definition of maculopathy it remains unclear which of the cases of maculopathy can be attributed to PPS. Second, the length of exposure to PPS is poorly defined. For example, the report of Ludwig et al.[13] is limited by its short follow-up and included patients with PPS who mostly had exposure of less than 5 years. Furthermore, PPS doses are often not specified. These studies, drawn from large cohorts of commercially insured patients, demonstrate a lack of a strong and reproducible association between PPS and maculopathy.

Analysis of the available information suggests an estimated prevalence of an association between PPS and maculopathy of between 2% and 4%. However, the published reports are based on highly selected cohorts and there is a significant risk that the associated data may not be representative. Thus, the true prevalence of pigmentary maculopathy associated with PPS remains speculative.

Evidence regarding disease progression or regression after cessation of PPS is limited. Imprecise characterisation of symptoms and premature drug cessation[10] currently preclude any meaningful conclusions being drawn.

Despite the lack of conclusive evidence on a causative relationship between PPS use and pigmentary maculopathy, public awareness and media interest have triggered an increase in reporting of possible side-effects. This is also reflected by the public data source for adverse events related to drugs, the FDA Adverse Event Reporting System (FAERS) database, which is used by the FDA and other entities for the post-marketing surveillance of medications and biologics. Since the launch of Elmiron in 1997, over 90% of all reports of eye disorders during PPS use were made between 2019 and 2021, and 99% of all maculopathies and retinal pigmentations were reported after the first publications in 2018.

CONCLUSION

This article reviews several case reports and case series reporting a unique maculopathy in patients with IC/BPS on PPS. The described clinical features and data from imaging studies support the notion of a new entity. However, with respect to the cause or the presumed association with exposure to PPS, the published data are suggestive but still inconsistent. Currently there are no prospective, well-researched, confirmatory data available.

A causal relationship cannot be established based on current epidemiological evidence,[53] due to variability in effect size, inconsistent diagnostic methodology, and the inability to prove temporality (the 'Bradford Hill criteria'). Most patients with the ocular finding of pigmentary maculopathy appear to have used high doses of PPS, occasionally above recommendation, over an extended period (around 15 years); however, the pathogenesis remains unexplained, and an unequivocal biological plausibility is still lacking.

The current lack of clear evidence does not exclude that this manifestation of pigmentary maculopathy is a true phenomenon; however, according to Doiron et al.,[54] several questions remain unanswered, such as are we truly observing a drug-associated toxicity or is the described maculopathy associated with another factor, e.g., another manifestation of IC/BPS itself.

Future controlled studies with sufficient follow-up to identify pigmentary changes that control for concomitant medications and comorbidities and assess for dose response are warranted. Studies should also observe the maximum daily dose of 300 mg. Consolidation of inclusion

criteria and a precise description of pigmentary maculopathy will enable the true incidence of this specific maculopathy in patients with IC/BPS who are receiving PPS.

PPS plays an important role in treatment of IC/BPS as it is the only oral drug approved for this indication. Weighing the risks and benefits of PPS use in patients with IC/BPS is essential. Clinicians should advise patients with IC/BPS of the reported potential association between PPS and pigmentary maculopathy, and to follow the recommended regimen of regular ophthalmological evaluation detailed in the product literature. Based on current evidence, PPS remains an effective, well-tolerated treatment for IC/BPS with appropriate monitoring.

Regarding ophthalmological care, recommendations are to pay particular attention to the unique ophthalmological features that single out pigmentary maculopathy from other maculopathies (described above). Screening for autofluorescence, RPE protrusions on OCT, and visual function is recommended. The value of visual field testing has not yet been established and is therefore not recommended. Liaison between ophthalmology and urology is also recommended in cases when corresponding findings are observed and ensure regular evaluation and careful monitoring of patients in cases when there is an uneventful screening.

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Predictive Value of Malignancy Index in Tumour Staging in Prostate Cancer

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Abstract

Background: A fine balance exists between the early treatment of a potentially lethal prostate disease and possible complications from the early treatment of a potentially indolent disease. Prostate-specific antigen (PSA) is an indicator of disease progression and is used in the clinical staging of prostate cancer (PCa). Given the arsenal of staging methods available, some intrusive, some not, is there a future for biochemical staging? As the presence and stage of disease are influenced by multiple factors, it is conceivable that an effective biomarker for determining pathology and stage could require a convolution of more than one biochemical entity. In this study, the authors introduce a malignancy index capable of staging PCa and discriminating pathology from non–pathology, in three unmatched sample types.

Methods: Total protein measurement was by means of the Pierce Bicinchoninic acid protein assay. The total PSA concentrations were measured using a microparticle enzyme immune assay, and ELISAs confirmed the urokinase plasminogen activator and plasminogen activator inhibitor–1 concentrations. The three markers (PSA, urokinase plasminogen activator, and plasminogen activator inhibitor-1 as well as patient age) were used in the formulation of a malignancy index (the degree of a person's vulnerability to disease).

Results: The authors examined the robustness of their malignancy index in transurethral resection and biopsy tissue and plasma samples and proved that it discriminated PCa from non–PCa and was able to predict tumour stage.
Conclusions: The malignancy index in this preliminary research increases with disease stage (T1 through T4) and deserves some attention as a credible marker.

Key Points

1. Prostate cancer staging is important for prognosis of the disease after determining its severity, and for determining the treatment course, however, staging continues to present challenges as not every patient will present with abnormal results in all tests.

2. In the present study transurethral and biopsy tissue and plasma samples were used in order to test the robustness of a malignancy index that discriminates prostate cancer from non–prostate cancer and its ability to predict tumour stage.

3. Despite a number of limitations, this study demonstrated that the malignancy index deserves some attention as a credible marker as it increases with disease stage (T1 through T4) across three independent prostate sample types.

INTRODUCTION

Prostate cancer (PCa) is the second most frequent cancer diagnosed in males and the fifth leading cause of death worldwide.[1] In the USA, the PCa death rate has dropped by approximately 4% each year from the mid-1990s to 2013, as a result of prostate-specific antigen (PSA) testing and advances in treatment, but this is no longer so.[2] PCa screening using PSA remains controversial due to the risk of over-diagnosis and over-treatment since many of the cancers diagnosed would remain asymptomatic, demonstrating that a protein whose expression is limited to specific tissues can be difficult to interpret at the clinical level.[3] Its specificity is limited by a high frequency of falsely raised values, and approximately two-thirds of all PSA values greater than 4 ng/mL in males older than 50 years are due to benign prostatic hyperplasia (BPH).[4]

A fine balance exists between the advantages of early treatment of a potentially lethal disease and possible complications from the early treatment of a potentially indolent disease. Apart from diagnosing PCa, the PSA assay is useful in tracking the progression of the disease and its response to treatment.[5,6]

Two studies found that 55% of males aged 46–84 years and diagnosed histologically with BPH had PSA values greater than 4 ng/mL.[7,8] It also emerged from their studies that 33% of patients with PCa showed low levels of PSA. These individuals would constitute a false-negative sub-group and may not receive treatment at all.

Limitations associated with PSA testing have led to a search for alternative biomarkers. Urokinase plasminogen activator (uPA) and its inhibitor, plasminogen activator inhibitor-1 (PAI-1), have been implicated in tumour aggressiveness and metastatic potential in breast cancer.[9-11] Clearly defined cut-off values of >3 ng/mg protein and >14 ng/mg protein for uPA and PAI-1, respectively, are linked with a poor outcome in node-negative breast cancer.[12,13] In fact, overexpression of PAI-1 is associated with a poor outcome in several cancers such as colon, thyroid, cervix, lung, and mouth, amongst others.[14-18] The clinical value of uPA and PAI-1 determination is, at present, still limited to breast cancer and no Level 1 evidence of benefit has been clinically demonstrated for these two markers in other malignancies. To date, no definitive role of the involvement of uPA and PAI-1 in prostate cancer has emerged.

In view of the association between breast cancer and PCa, and the similarity of their invasion process, the concentration of uPA and its inhibitor was determined in transurethral resection tissue (TURP), needle biopsies, and blood samples using ELISA methodology. The intention here being the search for a non-invasive prostate marker. A recent prostate needle biopsy study found that a PAI-1 value of ≥4.5 ng/mg protein in males of 60 years and older was moderately predictive for PCa, with a sensitivity of 63%.[19]

The uPA/PAI-1 ratio in surgical resections of prostate tissue was seen to discriminate prostate pathology from non-pathology but showed a dependence upon patient age.[7] This

separation was not apparent for needle biopsy tissue, where PAI-1 was seen to act as a sole PCa biomarker. Males 60 years of age and older with PAI-1 values above 3 ng/mg protein were more likely to have PCa.[8] This result did not hold entirely in a subsequent study, which led to the formulation of a malignancy index. On average, the malignancy index in TURP tissue, biopsy tissue, and plasma from patients with PCa was approximately 39-, 19-, and nine-fold higher, respectively, than that obtained from individuals with BPH and healthy volunteers.[20]

PCa staging can be either clinical or pathological. The former is based on the results of tests to determine the extent of the cancer and guide the treatment plan. The latter is based on what information is discovered after surgery and is likely the more accurate.[21]

Urological cancers are assessed universally by the tumour-node-metastasis system, which is considered the 'gold standard'.[22]

To adequately assess the patient's prognosis and plan the management, PCa staging must make use of the many clinicopathological parameters at its disposal.[23] These novel prognostic biomarkers aid in avoiding unnecessary imaging studies and invasive interventions.

It is well known that clinical staging suffers from the subjectivity of rectal examinations and variable imaging modalities.[24,25] The traditional PSA, and imaging and Gleason scores, may not accurately predict the patient's prognosis.[26] This has led to the search for biomarkers and PCa genetic alterations that may aid decision-making.[27] Emerging data has linked several germline DNA mutations to PCa but their value in the setting of PCa is unclear.[28]

In this study, using transurethral and biopsy tissue and plasma samples, the authors examine the robustness of a malignancy index that not only discriminates PCa from non–PCa but is able to predict tumour stage.

METHODS

Patient Eligibility Criteria

All consenting males presenting with a urologic problem (a raised PSA and enlarged prostate on digital rectal examination [DRE]) were eligible for the study. All consenting healthy male blood donors were also eligible and formed the control group.

Patients, Donors, and Sample Collection

The project was approved (reference: N09/11/330) by the Ethics Committee of the Faculty of Medicine and Health Sciences at the University of Stellenbosch, South Africa, and conducted in accordance with the Helsinki Declaration of 2013. Participants (who were Black, White, or of mixed ancestry) aged between 19 years and 86 years were included in the study. Patients and donors were recruited, and samples used in the study were collected over a period of 2 years (2014–2016).

Citrated blood samples were obtained from patients after signed consent and according to ethics guidelines. Care was taken when drawing the blood to avoid platelet activation and the release of platelet PAI-1. The samples were double-centrifuged at 1,500xG for 10 min, and platelet-free aliquots of plasma frozen at -80 °C. Haemolysed and lipaemic plasma samples were excluded. Patients and volunteers were recruited from the Tygerberg Academic Hospital, Cape Town, South Africa, and the Western Province Blood Transfusion Services, Cape Town, South Africa. Control samples and blood from patients diagnosed with PCa, based on PSA, DRE, Gleason score, and histopathology, were taken, as described elsewhere.[7,20]

Prostate needle biopsies and TURP were obtained from patients, after signed consent and according to ethics guidelines. Patients were recruited from the Gatesville Medical Centre, Cape Town, South Africa, and the Tygerberg Academic Hospital, Cape Town, South Africa. Patients were screened by PSA and DRE. An abnormal PSA and/or DRE finding resulted in the patient having an eight-core transrectal prostate biopsy. A histology positive score was added to the PSA and DRE scores to obtain a 10-point final score. For example, patients with a

negative DRE, a PSA value of 4 ng/mL, and one positive core received a rating of 1, indicating a low probability of PCa and a high probability of BPH. An unmistakably abnormal DRE with a PSA value of 100 ng/mL and one or more positive cores received a rating of 10, indicating a high probability of PCa and a low probability of BPH. The scoring system was not validated and, therefore, only patients who scored 8 or more in the PCa category were included. To reduce errors, the clinical data and patients' scores were reviewed by a second urologist. The scoring system was devised to obtain a high level of certainty of PCa identification, with a low probability of missing the same.

Measurement of Total Protein, Urokinase Plasminogen Activator, and Plasminogen Activator Inihibitor-1 Content

Aliquots of the protein extracted from the test samples were assayed by means of the Pierce Bicinchoninic acid protein assay (Thermo Fisher Scientific, Rockford, Illinois, USA). In brief, the total protein concentration is indicated by a colour change of the test solution from green to purple in proportion to protein concentration, which is then measured using a colorimetric technique. Confirmation of the uPA and PAI-1 content was by the Imubind® ELISA (Sekisui Diagnostics, Stamford, Connecticut, USA), as described elsewhere.[29] The total protein was expressed as mg/mL, while the uPA and PAI-1 content was expressed in ng/mg total protein. To test the ability of the pair of markers to predict disease state, uPA and PAI-1 concentrations were calculated for each sample, and the data for the PCa, BPH, and control groups compared.

Measurement of Total Prostate-Specific Antigen

The AxSYM® (Abbott Laboratories, Illinois, USA) total PSA in patient and control sera was measured using a microparticle enzyme immune assay and expressed as ng/mL. Since it was not required for healthy volunteers (controls) to have a PSA test, age-matched PSA levels (mean: 0.93 ng/mL; range: 0.38–3.25 ng/mL), were used for the control group, as reported elsewhere.[30] This was found to correlate with published in-house PSA data (mean: 0.9312 ng/mL; range: 0.12–3.30 ng/mL) for controls.[31]

Malignancy Index

The rationale behind the malignancy index resulted from the observation of unusually high PAI-1 values in needle biopsies from patients with BPH, analogous to false-positive PSA values. Controversy surrounding PSA, and no level of evidence existing for PAI-1 and uPA, other than in node-negative breast cancer,[11] prompted the integration of the three biomarkers and age in a malignancy index (in units of mal: 1 mal=1 $ng^3 \times [mg\ protein]^{-2} \times ml^{-1} \times y^{-1}$), as defined, below:[20]

Malignancy index=([PSA]x[uPA]x[PAI–1])/age

STATISTICAL ANALYSIS

Statistical analyses were performed using GraphPad Prism scientific graphing and statistics software (GraphPad Software, San Diego, California, USA). To compare the data sets, the unpaired t-test was used, and p-values were calculated from two-sided tests. A value of <0.05 indicated a statistically significant difference between the data sets.

RESULTS

The age distribution of the participants is presented in Table 1. For the plasma group, disease progression appeared to be correlated with age, with elderly patients presenting with advanced disease. The control cohort of this group was significantly younger than patients of all stages ($p<0.0001$), possibly because the majority (approximately 76%) of the former were aged ≤60 years. In the biopsy group, elderly patients also tended to present with advanced disease (with p-values decreasing from 0.7906 to 0.0089). No relationship was apparent between age and disease stage in the TURP group.

Figure 1 shows the comparison of malignancy indices in units of mal ($ng^3 \times [mg\ protein]^{-2} \times ml^{-1} \times y^{-1}$) in plasma samples from the controls, males diagnosed with BPH, and those in various stages of PCa. The malignancy index significantly separates the BPH group from the control group, with a value of 0.0016 (p=0.0346). Plasma samples from stage T1 notwithstanding (p=0.2544), stages T2 through T4 are seen to be significantly different to the control group (n=110), with values of 0.0200 (n=42; p=0.0003),

Table 1: Age distribution among the studied participants.

Histology	Tumour Stage (n; p)					
	Control	BPH	T1	T2	T3	T4
Plasma	49.50±1.47 (110; n.d.)	65.10±1.76 (20; <0.0001)	64.91±1.50 (32; <0.0001)	65.72±1.18 (42; <0.0001)	68.56±1.58 (18; <0.0001)	67.36±1.91 (26; <0.0001)
Biopsy	N/A	64.30±0.71 (112; n.d.)	64.66±1.22 (44; 0.7906)	65.81±1.49 (32; 0.3301)	68.37±1.53 (19; 0.0289)	70.73±2.63 (11; 0.0089)
TURP	N/A	67.80±0.72 (114; n.d.)	65.33±2.15 (8; 0.3919)	66.00±2.03 (5; 0.6059)	72.00±4.41 (4; 0.2394)	68.30±2.59 (12; 0.8433)

Comparison with the respective controls (control group for plasma; BPH for biopsy and TURP) and the number of participants. Some of the p-values were not determined as group was used as a comparator.

BPH: benign prostatic hyperplasia; N/A: not applicable; n.d.: not determined; TURP: transurethral resection tissue.

0.0927 (n=18; p<0.0001), and 0.1920 (n=26; p<0.0001), respectively. The malignancy index is seen to rise with tumour stage.

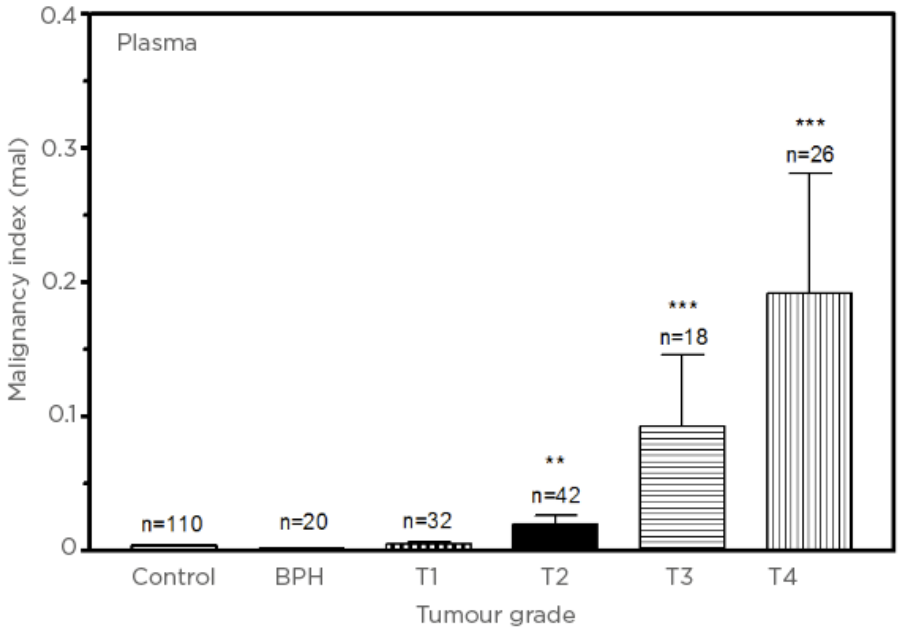
Figure 2 shows the comparison of malignancy indices in biopsy tissue from patients diagnosed with BPH and PCa. The malignancy indices increase with tumour stage, from 0.2003±0.0903 (T1) to 26.08±15.56 (T4). Interestingly, the index for the patients with BPH using biopsies was lower than for patients with T1 PCa. This appears to be consistent with the finding that the index is higher in the healthy donors than in patients with BPH for the plasma analysis (Figure 1). While the differences between malignancy indices of T1 (p=0.2439) and T2 (p=0.1466) PCa and the BPH group did not reach statistical significance, those for patients with T3 (p=0.0007) and T4 (p<0.0001) PCa were significant. The large errors in the PCa groups are associated with outlier marker values.

Given the small PCa samples across tumour stages for TURP, the malignancy indices are, nevertheless, seen to rise with tumour stage, from 0.0255±0.0115 (T1) to 8.302±3.423 (T4 [Figure 3]). Relative to the BPH group, the increases in the indices of patients with T2, T3, and T4 PCa were statistically significant (p<0.0001). As in the case of the biopsy experiment (Figure 2), the index for the patients with BPH emerged lower than for patients with T1 PCa (p=0.2062).

DISCUSSION

PCa staging is important for evaluating the prognosis of the disease after determining its severity, and guiding patient treatment.[32] Staging can be either clinical or pathological. The former uses data when the patient is diagnosed to estimate the extent of the disease. The latter, more accurate method, involves the pathological examination of tissue after surgery to assess the extent of the disease.[33] However, staging continues to present challenges to clinicians as not every patient will present with abnormal results in all tests. Radiological imaging such as MRI has contributed immensely to the staging of PCa in primary and post-treatment settings.[34,35] Another is the prostate specific membrane antigen (PSMA) PET–CT scan, in which high-affinity gallium-68-labelled and fluorine-18-labelled ligands bind to PSMA, an antigen expressed in prostate cancer and metastases.[36] PSMA PET–CT scans cost anything from 20,000 Indian Rupees to 35,000 Indian

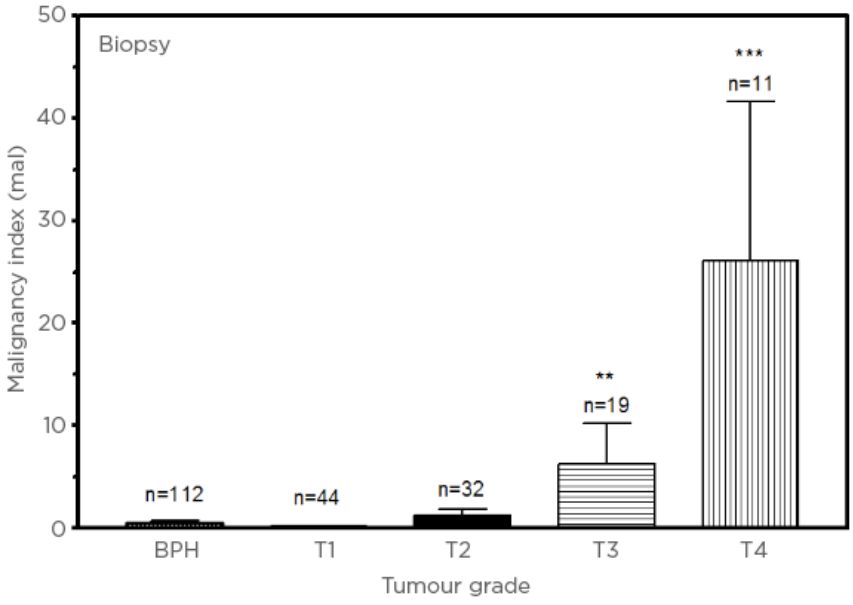
Figure 1: Comparison of malignancy indices (in units of mal: 1 mal=1 $ng^3[mg\ protein]^{-2}ml^{-1}y^{-1}$) in control, benign prostatic hyperplasia, and Stage T1–T4 prostate cancer plasma samples.



Plasma data (mean±SEM), compared with the control group for statistical significance.

BPH: benign prostatic hyperplasia; SEM: standard error of mean.

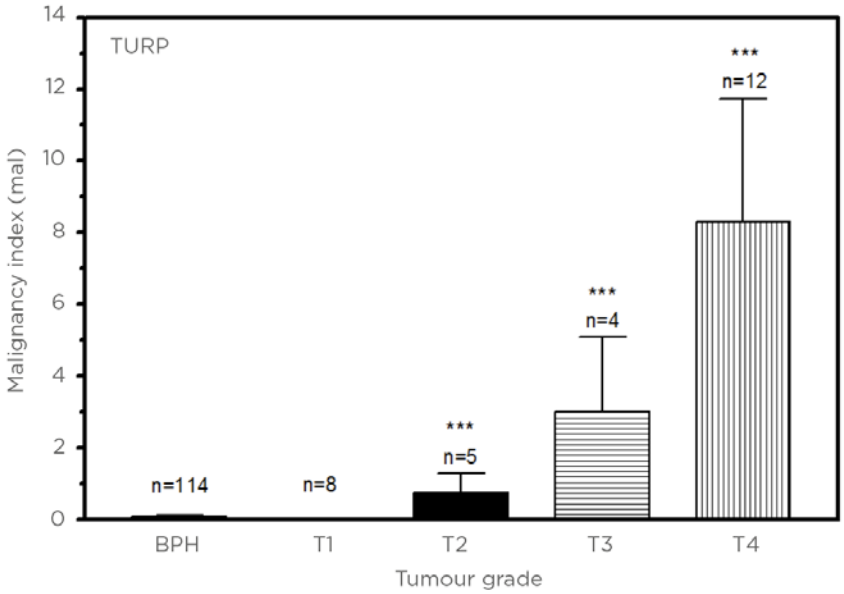
Figure 2: Comparison of malignancy indices (in units of mal: 1 mal=1 $ng^3[mg\ protein]^{-2}ml^{-1}y^{-1}$) in benign prostatic hyperplasia and Stage T1–T4 prostate cancer biopsy samples.



Biopsy data (mean±SEM), compared with BPH group for statistical significance.

BPH: benign prostatic hyperplasia; SEM: standard error of mean.

Figure 3: Comparison of malignancy indices (in units of mal: 1 mal=1 ng^{3}[mg protein]$^{-2}$ml^{-1}y^{-1}) in benign prostatic hyperplasia and Stage T1–T4 prostate cancer transurethral resection tissue samples.



TURP data (mean±SEM), compared with BPH group for statistical significance.

BPH: benign prostatic hyperplasia; SEM: standard error of mean; TURP: transurethral resection tissue.

Rupees (Bookmyscans, Bangalore, India), which is outside the medical budget allocation of poorly resourced countries, as are many of the imaging tests.[37]

Whither, then, biochemical markers? PCa is a heterogeneous disease, and finding one marker capable of replacing the several examinations currently employed to stage prostate cancer patients is wishful thinking.[38] Nonetheless, the search continues for markers capable of predicting a patient's stage and response to treatment.

Increased angiogenesis is a feature of cancer metastasis and a prime target for treatment since vascularisation leads to tumour growth and invasion. Tumour-associated angiogenesis is directed by particular cytokines, such as IL-6 and TGF-β1.[39] IL-6 is also an agent of chronic inflammation in PCa and is reported to play a key role in castration-resistant PCa.[40]

In a breast cancer study by Ravishankaran and Karunanithi,[41] serum IL-6 levels were seen to increase appreciably with tumour stage. Alchalabi et al.[42] showed a strong association between IL-6 levels of 70.5, 92.0, 155.7 and 237.5 pg/mL and tumour stage T1 through T4, respectively, in bladder cancer. Mroczko et al.[43] showed increased IL-6 levels in line with tumour stage, which was statistically significant in a pancreatic cancer study. In a gastric cancer study by Lukaszewicz-Zajac et al.,[44] serum IL-6 levels also increased in line with tumour stage but the differences were not deemed statistically significant.

A study on gastric cancer by Tüzün et al.[45] showed that TGF-β1 levels were seen to be significantly higher in stages T2, T3, and T4 but not in stage T1 or the controls. Shim et al.,[46] in a colorectal cancer study, showed a significant increase in TGF-β1 levels across all four tumour stages, of 31, 40, 46, and 54 ng/mL, respectively. In a differentiated thyroid cancer study by Zivancevic–Simonovic et al.,[47] no significant differences in serum TGF-β1 levels between the patients with differentiated thyroid cancer and the controls was noted. Some studies have shown an increase, then, in serum TGF-β1 levels in different cancers, and others a decrease.[48,49]

What, then, of IL-6 and TGF-β1 levels in prostate cancer? Wolff et al.[50] found that TGF-β1 levels did not discriminate PCa from BPH, and that it did not increase with advancing tumour stage. An earlier study by Perry et al.[51] found that TGF–β1 levels did not discriminate the PCa group from the control group and that there was no correlation with either PSA value or tumour stage. In subsequent studies by Shariat et al.,[52,53] increased TGF-β1 levels in PCa tissue samples, post-prostatectomy, were shown to be indicators of heightened disease grade and stage.

Kattan et al.[54] proposed adding both IL-6 and TGF-β1 to the existing arsenal of clinical markers, which improved their ability to predict the biochemical progression of PCa.

In this study, using transurethral and biopsy tissue and plasma samples, the robustness of a malignancy index that not only discriminates PCa from non–PCa but is also able to predict tumour stage is also examined. This preliminary research shows that the malignancy index increases with disease stage (T1 through T4) across three independent prostate sample types, albeit with the limitation of not being matched, and deserves some attention as a credible marker. Given that the malignancy index incorporates three markers, the large error margins noted are associated with occasional outliers, or steep PSA and PAI-1 values. A potential source of bias could be the significant disparity in sample sizes between control group for plasma (or BPH groups for biopsy and TURP) and disease stage (Table 1). Of specific note are those for TURP, where tumour stages numbers as low as 4–12 are compared with a BPH group of 114. Such unmatched sample sizes can skew the statistics in favour of the larger group. Also, the control group of healthy donors for the plasma analysis were much younger than their BPH and PCa counterparts and could inherently exhibit lower marker levels, and thus low malignancy indices.

Another limitation and potential confounder of this study is the inevitable use of BPH groups as controls for the biopsy and TURP analyses. Use of true controls from healthy donors, although invasive and unethical, could lead to different and possibly stronger conclusions. Interestingly, malignancy indices were negligible (data not shown) in prostate biopsy samples derived from patients with pathologies other than PCa or BPH (i.e., atrophic prostate, inflammation, chronic prostatitis, hyperplasia of the bladder). As these non–PCa or non–BPH pathologies could potentially be confounders in the selectivity of any diagnostic tool for PCa, the observation that their malignancy indices are miniscule further emphasises the robustness and discriminatory power of this novel biomarker.

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Robotic-Management for Renal Cell Carcinoma with Venous System Involvement at a Community Hospital: Case Series

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Abstract

Background: Kidney cancer accounts for 2.6% of all visceral malignancies in the USA. Around 5–10% of patients with renal cell carcinoma (RCC) have renal venous involvement. Open nephrectomy with tumour thrombectomy has classically been the gold standard for treatment of these masses. As opposed to open surgery, minimally invasive surgery is associated with less intraoperative blood loss, shorter hospital stays, and lower complication rates. In this study, the authors present a series of robotic radical nephrectomies in patients with renal venous invasion.

Materials and methods: Between November 2016 and March 2021, 10 patients with RCC with renal venous invasion underwent radical nephrectomies. In eight patients, renal venous invasion was evident based on CT. In four cases, tumour thrombus invaded the inferior vena cava. In three of these cases, the tumour thrombus was able to be milked back into the renal vein, allowing for ligation and transection in the standard fashion. In the remaining case, cavotomy and tumour thrombus extraction was required.

Results: All cases were performed completely robotically, without requiring open conversion. Median operative time was 136 minutes. Median estimated blood loss was 450 mL. Median length of hospitalisation was 2.5 days. Eight patients had no complications following the procedure.

Conclusion: In the setting of a community hospital, robotic management of patients with T3a and T3b RCC with venous invasion is a safe and effective alternative to open surgery.

Key Points

1. Minimal invasive renal surgery has advanced considerably over the last decade and has demonstrated several benefits such as intra-operative blood loss, decreased length of stay, and reduced post-operative analgesia requirements.

2. In this case report series, the authors perform radical nephrectomies in 10 patients with either T3a or T3b renal cell carcinoma and renal venous invasion in a community hospital.

3. Open surgery presents several complications including longer hospital stays; however, robotic management of renal tumours with venous invasion can be performed safely and effectively.

INTRODUCTION

Kidney cancer accounts for 2.6% of all visceral malignancies in the USA, with renal cell carcinoma (RCC) comprising the vast majority.[1] Classic presentation of RCC includes the triad of flank pain, haematuria, and a palpable abdominal mass. However, it is now more common for RCC to be discovered incidentally on imaging or following the workup for haematuria. Risk factors include smoking, obesity, hypertension, chronic kidney disease, and inherited disorders such as Von Hippel–Lindau or polycystic kidney disease.[2] Biopsy of lesions found on CT suspicious for kidney cancer is controversial, and masses are often definitively managed with surgical removal.[3] As the disease progresses, the renal venous system can be compromised by the tumour and growth may continue to the inferior vena cava (IVC) and right atrium. Pathologic T3a+ disease with renal vein involvement is seen in 4–10% of all patients with RCC.[1] The gold standard treatment for T3a+ disease is nephrectomy and tumour thrombectomy.[4] Unfortunately, the 5-year cancer-specific survival rate is only 25–53%, which portends a worse prognosis than localised RCC.[1] Conventionally, open nephrectomy with tumour thrombectomy has been the standard of care for treatment of masses with venous invasion. However, it has become increasingly common for these masses to be treated with minimally invasive surgery (MIS).[4] MIS has been shown to have less intraoperative blood loss, shorter hospital admissions, improved time to convalescence, and lower complication rates than open surgery.[5] While many previous studies detailed the use of MIS at tertiary academic centres, the goal of this case series is to demonstrate robotic management of RCC with renal vein or IVC involvement at a community hospital.

MATERIALS AND METHODS

Following institutional review board approval, this study represents a monocentric, retrospective review of robotic assisted nephrectomies with or without IVC thrombectomy. All operations were performed by a single high-volume robotic surgeon (Maatman) from November 2016 to March 2021. A total of 59 cases were completed by the primary surgeon between this time. Thirty-seven patients were selected who were at least 18 years or older and had final pathologic staging of T3a or greater. Of these patients, only 10 patients had venous invasion and were included for final analysis. The remaining 27 were excluded because they had either perinephric or collecting system invasion without venous involvement on final pathology. All patients included in the study had CT imaging obtained perioperatively.

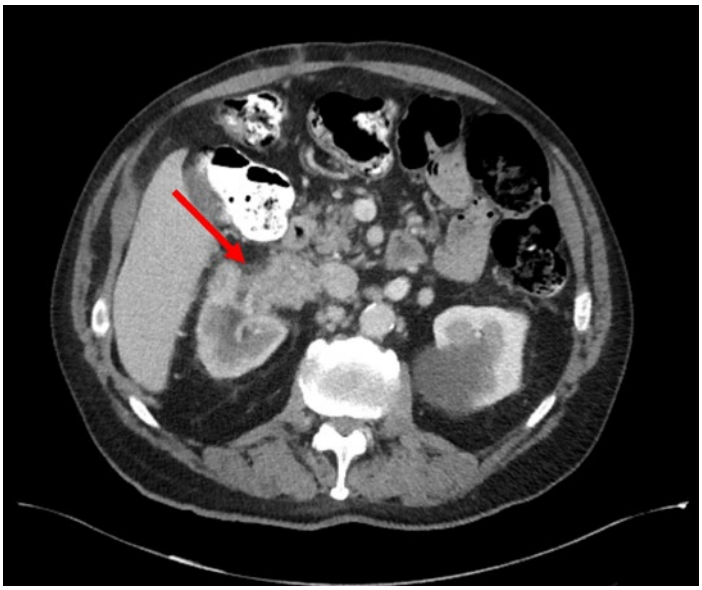
Data collected included patient demographics (age, laterality, comorbid factors, BMI, and American Society of Anesthesiology [ASA] score); intraoperative estimated blood loss, operative time, and postoperative factors (length of stay, postoperative complications) as well as final pathology. Preoperative imaging was also reviewed by institutional board-certified radiologists to evaluate for gross involvement of the renal venous system. A complete breakdown of patient demographics is demonstrated in Table 1.

Table 1: Patient demographics and preoperative characteristics.

Patient	Age	Gender	Side	Renal venous involvement on CT	Medical comorbidities	BMI	ASA classification
1	53	Male	Right	No	HTN	32.20	2
2	56	Male	Right	Yes	HTN	40.50	2
3	58	Male	Right	Yes	HLD	34.55	3
4	61	Female	Right	Yes	CAD, HLD	23.25	3
5	71	Male	Right	Yes	CAD, HLD, HTN, IIDM	29.50	3
6	74	Female	Right	Yes	None	20.36	3
7	77	Male	Right	Yes	None	17.36	3
8	78	Male	Right	No	HLD, HTN	26.60	2
9	81	Male	Right	Yes	HLD, HTN, hypothyroidism	30.15	3
10	87	Male	Right	Yes	HLD, HTN, PAD, IIDM	26.83	3
Average	69.6	N/A	Right	N/A	N/A	28.13	2.7

ASA: American Society of Anesthesiologists; CAD: coronary artery disease; HLD: hyperlipidaemia; HTN: hypertension; IIDM: insulin-independent diabetes mellitus; N/A: not applicable; PAD: peripheral artery disease.

Figure 1: Axial CT imaging of a patient's abdomen, demonstrating tumour thrombus invading the right renal vein and inferior vena cava.



Tumour thrombosis measured 10×8×4.5 cm.

SURGICAL TECHNIQUE

The da Vinci Si and Xi Surgical Systems (Intuitive, Sunnyvale, California, USA) were used for all cases. Each case was started by medialising the colon and exposing the renal hilum. In almost every case a gross tumour thrombus was visible in the renal vein. The renal artery was then exposed, ligated, and transected. After transection of the renal artery, the treatment algorithm would diverge based on the involvement of the tumour thrombus. In those with tumour thrombus extending only into the renal vein, a robotic stapler was used to ligate the vein after ensuring mobility of the tumour thrombus and ability to maintain a satisfactory margin (Figure 1).

Thrombus Extension That Does Not Require Cavotomy

When gross tumour thrombus was seen extending into the IVC, dissection was performed down to the level of the iliac bifurcation. A vessel loop was then wrapped doubly around the IVC below the level of the thrombus. The IVC superior to the thrombus and the left renal vein were mobilised and vessel loops were placed around these vessels in a similar fashion. Following placement, the vessel loops were pulled through 24 Fr Foley catheter rubber shods. In the event vascular occlusion was needed, the Rummel tourniquets would be able to be cinched down and secured with Hem-o-lok clips (Teleflex®, Wayne, Pennsylvania, USA). In almost all of these patients, occlusion was not needed, and the tumour thrombus was able to be pressed into the renal vein by serially grasping the proximal edge of the thrombus.

Thrombus Extension Requiring Cavotomy

In one of the patients, the thrombus was unable to be mobilised back into the renal vein and access into the lumen of the IVC was deemed necessary. The Rummel tourniquets were then used to secure the vasculature as previously described. Next, the IVC was sharply dissected open, and the tumour thrombus was extracted. The IVC was closed with running 3–0 silk suture. The tourniquets were released, haemostasis was confirmed. The kidney was then dissected free, and the procedure was completed in the standard fashion.

RESULTS

All cases were successfully performed robotically without conversion to open. Mean patient BMI was 28.2 (range: 17.4–40.5) and mean ASA score was 2.7 (range: 2–3). All additional preoperative patient characteristics are listed in Table 1. Of note, all patients had right sided disease.

In eight cases, gross tumour thrombi were visibly extending into the renal vasculature on CT (Figure 1). In two cases, the preoperative imaging was not suggestive of thrombus and the venous extension was discovered at the time of pathologic evaluation. Surgical margins were negative in eight patients and positive in two. The two patients with positive margins had T4 disease radiographically. For one of these patients, the procedure was performed for palliative purposes for multiple life-threatening episodes of haematuria. The second patient with T4 disease and a positive margin had a cytoreductive nephrectomy to prepare for systemic chemotherapy.

Eight patients had no complications according to the Clavien–Dindo classification. One patient had a Clavien Grade II for acute blood loss anaemia, requiring blood transfusion. Another patient had a Clavien Grade IIIa as they required readmission and nasogastric tube placement for a postoperative ileus. Nine of the 10 tumours were clear cell RCC and one was papillary RCC. The median blood loss was 450 mL (60–900), the median length of inpatient stay was 2.5 days (1–4), and the median operative time was 136 minutes (97–191 [Table 2]). In three cases, the tumour thrombus was able to be milked back into the renal vein from the IVC prior to ligation. In one case tumour thrombus extension into the IVC required cavotomy as the thrombus was unable to mobilised.

DISCUSSION

The first laparoscopic radical nephrectomy was performed in 1990 on an 85-year-old female with a 3 cm mass. It took 7 hours, and the patient was discharged on post-operative Day 6.[6] Since then, minimally invasive renal surgery has advanced considerably, and the approach has been widely adopted. Significant benefits over open surgery have been demonstrated including

Table 2: Postoperative outcomes.

Patient number	*Pathological stage	Tumour size (cm)	Margin status	Robotic time (mins)	EBL (mL)	Length of stay (days)	Complication
1	pT3a Nx	6.0×4.5×7.0	Negative	136	478	3	Readmission for postoperative ileus
2	pT3b Nx	8.0×6.0×5.0	Negative	154	900	4	None
3	pT3a Nx	10.0×8.0×4.5	Negative	114	500	2	None
4	pT3a Nx	7.5×7.4×6.1	Negative	97	60	2	None
5	pT3b N0	6.7×5.2×3.0	Negative	112	80	1	None
6	pT3a N1	15.0×9.0×13.0	Negative	191	900	4	Acute blood loss anaemia, transfusion required
7	pT3a N1	7.3×5.5×4.0	Renal vein margin positive	110	850	4	None
8	pT3a Nx	4.7×4.3×3.4	Negative	100	140	1	None
9	pT3a N0	12.0×8.0×6.0	Negative	184	250	3	None
10	pT3a Nx	7.3×6.0×6.0	Renal vein margin positive	162	350	2	None
Average	N/A	N/A	N/A	136	450.8	2.6	N/A

**Pathological staging based on the American Joint Committee on Cancer (AJCC) classification.*

EBL: estimated blood loss; pT: pathologic tumour; N: nodes; N/A: not applicable.

less intraoperative blood loss, decreased length of stay, and reduced postoperative analgesia requirements.[6] The utilisation of the laparoscopic approach peaked in 2008 when it neared 50% of all cases. In 2004 the first report of a robot assisted radical nephrectomy was published, and this approach continues to increase in popularity. As many as 27% of all radical nephrectomies were performed robotically in 2015.[7] Some argue that a purely laparoscopic approach is the optimal method to perform a radical nephrectomy as the robotic approach is more expensive and does not have significantly improved outcomes.[7] At the authors' institution, they prefer to use the robotic approach as it allows the trainees to hone their skills for other robotic procedures such as partial nephrectomies, nephroureterectomies, and pyeloplasties.

Analysis of the literature demonstrates that perioperative outcomes related to RCC with IVC thrombus are often associated with complications. In one study of 5,180 patients from 416 institutions, 4% of patients had a major postoperative complication, 28% had a complication of any kind, more than 40% of patients had an operative time of greater than 4 hours, 20% of patients required a blood transfusion, and 20% of patients required hospitalisation for more than 4 days.[8] In this study's series, only one of the patients required transfusion (12.5%), operative time never exceeded 4 hours, and length of stay never exceeded 4 days.[7] All of the tumours in this series except one were at least 7 cm in diameter and almost all had gross extension of tumour thrombus. Even in those with large tumour burdens, this series confirms safety and

efficacy in the treatment of these patients in a community setting.

In two patients, renal venous invasion was discovered during pathologic processing. As a result of this finding, both of their T stages were upgraded from T1 to T3. In one study of 987 patients with cT1a tumours, 9% were upstaged to pT3a as a result of renal venous invasion on pathology. These patients were found to have lower 2-year recurrence free survival (87.3%) than those that were not upstaged (98.7%).[8] This finding was redemonstrated in a study of almost 2,000 patients at the University of Michigan, USA, in 2018. Russell et al.[9] found both the 3-year and 5-year recurrence free survival of upstaged tumours to be significantly lower than those of their matched non-upstaged cohort members. The difference in 5-year progression free survival was particularly drastic with the non-upstaged progression free survival rate of 96% compared to the upstaged progression free survival rate of 76%.[9]

In the staging of RCC, the grade of T3a can be quite variable. The size of the tumour is no longer a factor, and the primary determinant of staging is the degree of extra renal extension. Extra renal extension can occur in multiple places including renal sinus fat, renal venous system, or perirenal fat. As these tumours can have various sizes and types of invasion, their prognosis can vary significantly. Renal venous thrombosis (RVT) is a particularly poor prognostic factor and is a predictive factor for postoperative recurrence in patients with T3. One study of 800 patients found that those with clinically detected RVT had a 5-year recurrence free survival rate of 24.9% as opposed to 74.7% in other patients with T3a disease.[8] They also found that those with RVT had a 5-year cancer specific survival rate of 70.5% compared with 92.6%.[8]

The study represents a community-based, single institution's results, and operative techniques in those undergoing radical nephrectomy with renal venous invasion. Primary limitations of this study include its retrospective nature, only single surgeon performing all the cases, and the small sample size. The sample size is limited as RCC with significant venous invasion is relatively rare. Selection bias is an additional limitation as those with T3 disease that were poor candidates for surgery were not operated on.

CONCLUSION

Traditionally, renal tumours with gross tumour thrombi have been treated with open surgery, especially outside of the setting of a large academic hospital. Open surgery is associated with longer hospital stays, more postoperative pain, greater blood loss, and higher complication rates. This case series demonstrates that the robotic management of renal tumours with venous invasion can be performed safely and effectively in a community setting.

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Giant Urinary Bladder Stone in a Middle-Aged Male

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Abstract

Urolithiasis is a disorder that affects 10–15% of people at least once in their lives. Among the calculi affecting the urinary tract are the bladder stones. Giant urinary bladder stones are rare and can potentially lead to the onset of intense symptoms as well as life threatening repercussions. This disorder demands an accurate diagnosis with the use of imaging tools and laboratory tests, as well as an agile and appropriate therapeutic approach in order to prevent unfavourable outcomes. This paper reports on a bladder stone that was 18.5 cm in diameter and weighed 1.328 kg, which was extracted from a middle-aged male.

Key Points

1. Urolithiasis is a disorder that affects 10–15% of people at least once in their lives; giant bladder stones account for only 1% of urolithiases.

2. In this study, the authors reported a urinary bladder stone with the largest diameter ever described, with 185 mm diameter and 1.328 kg in weight.

3. Laparoscopic surgery and robotic cystolithotomy are suitable procedures for the removal of bladder stones. Cystolithotomy is the preferred procedure for the treatment of giant calculi.

INTRODUCTION

Approximately 10–15% of the general population is affected by urolithiases at least once in their lifetime.[1] Having a giant urinary bladder stone is a particularly rare condition and its development is usually associated with disorders that promote urinary stasis.[2] This type of urolith can lead to serious health repercussions, including hydronephrosis and kidney failure.[3] However, despite being a life threatening urological disease, scientific evidence on this issue remains

sparse. Here, the authors report the occurrence of a bladder stone that was 18.5 cm in diameter and weighed 1.328 kg in a middle-aged male. To the authors' knowledge, this is the bladder stone with the largest diameter reported to date. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

CASE REPORT

The case was a 51-year-old male patient with no previous relevant medical history, who attended to a medical consultation on 22nd March 2019, complaining of hypogastric pain and intermittent haematuria. He had no history of urinary tract infections, previous surgeries, or any factor suggesting neurogenic bladder, benign prostatic hyperplasia, and urethral stricture. On physical examination, he had a firm, mobile, hypogastric mass. Serum analysis revealed mild normocytic and normochromic anaemia (haemoglobin: 12.6 g/dL). Moreover, urinalysis evidenced slightly cloudy urine, proteinuria (1+), leukocyturia (2+), ketonuria (1+), haemoglobinuria (2+), pyuria (20 piocytes/field), haematuria (18 red blood cells/field), and rare epithelial cells. No bacterial growth was observed in the final culture. Ultrasound imaging (USI) of the abdomen demonstrated a large mass inside the urinary bladder, with posterior acoustic shadowing, suggesting a giant bladder stone. The USI also evidenced marked hydronephrosis on the right (Grade III/IV) and mild hydronephrosis on the left (Grade I/IV) as well as bilateral proximal ureteral dilatations. The sizes of the prostate and its medial lobe were not increased. The residual post-voiding volume was 184.5 mL (Figure 1). Nine weeks later, the patient underwent a cystolithotomy, with removal of a stone measuring 185 mm at its largest diameter and weighing 1.328 kg (Figure 2). The surgery was performed through an 18 cm infraumbilical incision due to the stone size. There was no insertion of a suprapubic catheter and no retrograde cystogram was available. Urethral catheterisation was performed. On the second postoperative day, he underwent an abdominal CT for an ileus investigation and to discard

Figure 1: Ultrasound images of the urinary bladder with the giant bladder stone inside, which is represented by a hyperechoic image with acoustic shadowing.

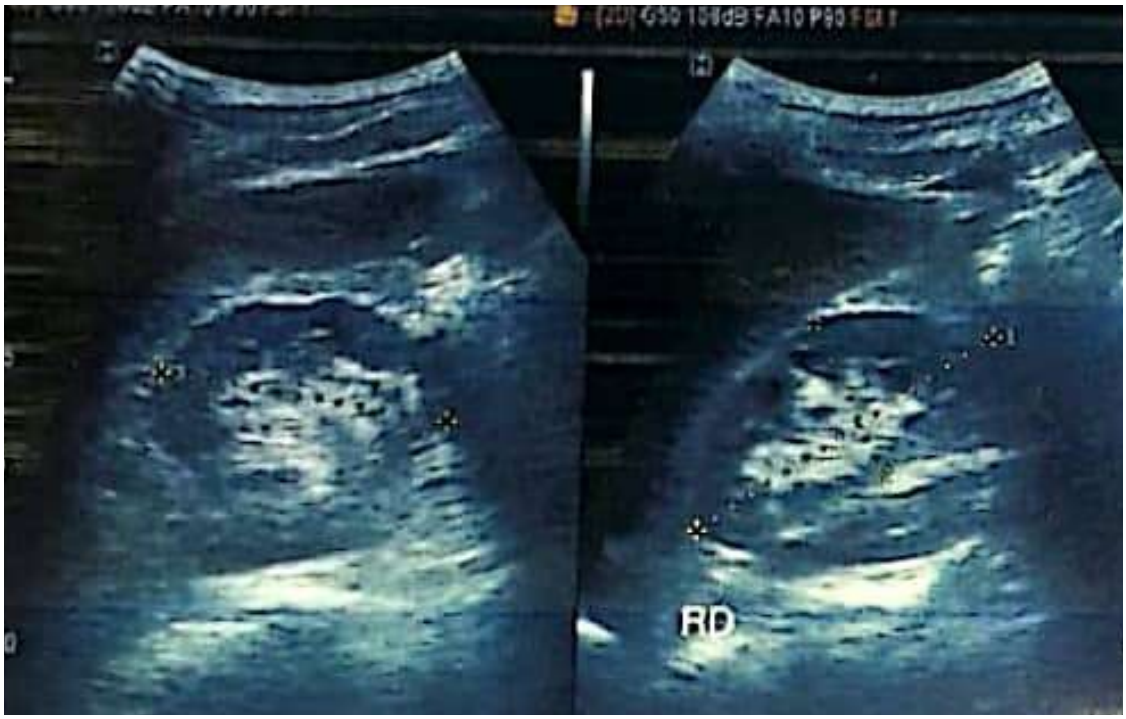
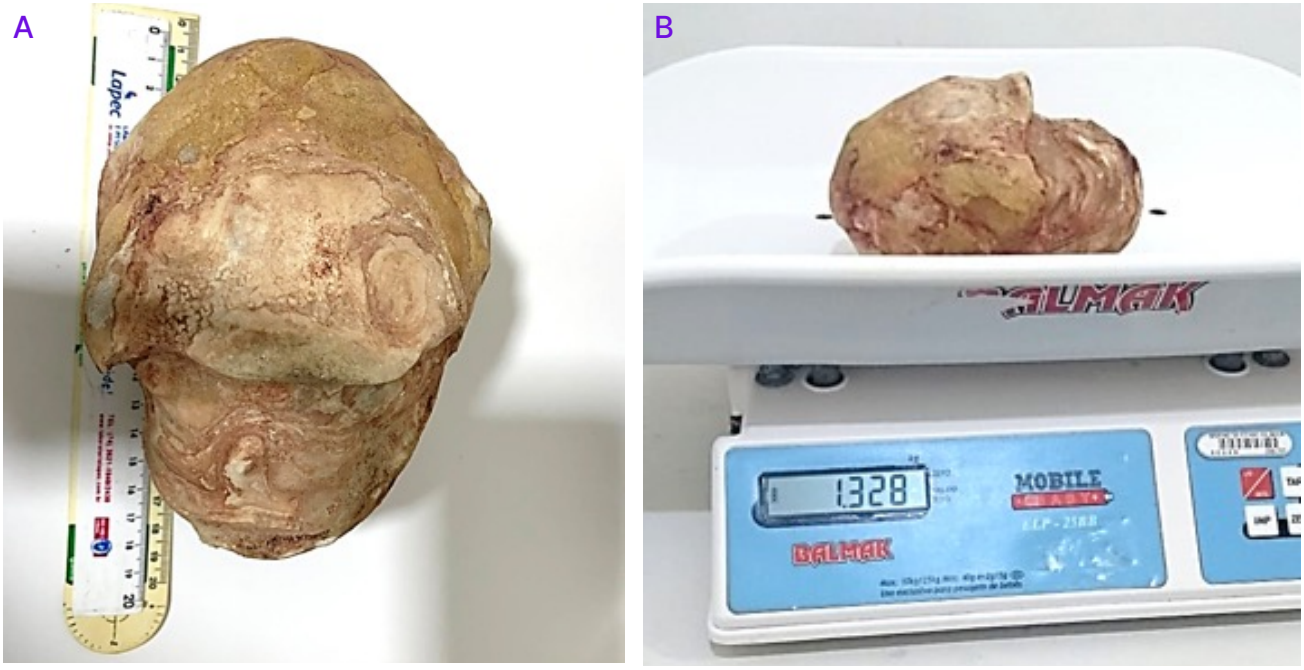


Figure 2: Pictures demonstrating the (A) diameter (18.5 cm) and (B) weight (1.328 kg) of the giant bladder stone removed from the patient.



the possibility of intestinal perforation. The CT evidenced a urinary bladder with enlarged dimensions as well as a diffuse, remarkable wall thickening. In addition, a heterogeneous material inside the bladder was observed, originating iso/hypoattenuating images suggesting gaseous foci and small stones (at least five stones smaller than 0.3 cm and one with 0.5×0.5×0.7 cm). A minor ectasia was found in the right pyelocaliceal system. The patient had a satisfactory recovery with no further complaints, and he was discharged on the fifth postoperative day.

DISCUSSION

Bladder stones represent approximately 5% of urinary tract calculi, and giant bladder stones account for only 1% of urolithiases.[4,5] Of note, the incidence of vesical calculi is higher in developing countries and this condition is responsible for 8% of urolithiasis-related deaths.[6] This phenomenon occurs mainly among males, who represent 95% of cases.[7] Bladder stones can be classified into primary and secondary. The former develops without any known abnormality that facilitates stone formation. The latter are preceded by a recognisable aetiologic cause. Disorders favouring urinary stasis and, consequently, the precipitation of calcium, oxalate, phosphate, and uric acid predispose the formation of bladder stones. Among these conditions, benign prostatic hyperplasia, urethral stricture, and neurogenic bladder stand out.[8]

Besides male gender, no other risk factor for the occurrence of bladder stones was identified in the authors' patient, who probably had a primary bladder stone. Of note, the occurrence of primary bladder stones has been associated with low socioeconomic status and cereal-based diets, which may lead to metabolic repercussions including increased acid uric levels, hypophosphaturia, and hyperammoniuria.[9]

Regarding chemical characteristics, most bladder stones have mixed composition, and these properties are influenced by pH, degree of urine saturation, and possible micro-organisms in the urine. Bladder calculi are mostly made up of uric acid and urate. The presence of Proteus in the urine has been associated with calcium phosphate and struvite stones, whereas Escherichia coli has been related to the

occurrence of calcium oxalate and urate calculi.[6] Unfortunately, the study of stone composition was not performed in the case reported here.

Complaints of occasional haematuria and suprapubic pain are often observed in individuals with bladder stones, and they were present in the aforementioned case. Furthermore, patients frequently refer to urinary symptoms and urinary urgency.[10,11] USI of the bladder is considered the first choice for bladder stone diagnosis due to its broad availability, whereas cystoscopy has the highest accuracy in the detection of this disorder since the former may not distinguish bladder calculi from tumours on some occasions. The calculi may also be detected through X-rays, but 50% of the bladder stones are radiolucent.[12]

A CT scan was performed in the authors' case for a post-surgical evaluation of an ileus, but this method is not often used as a diagnostic tool for bladder lithiasis as performing cheaper imaging methods is more advantageous in this clinical scenario.[11] Since bacterial colonisation favours lithogenesis and bladder calculi predispose to infection, it is useful to perform a urine culture test, which did not verify bacterial growth in the authors' case.[12] Hydroureter and bilateral hydronephrosis are rare outcomes in individuals with bladder lithiasis.[13] The occurrence of these repercussions in the present case was probably due to the huge size of the calculus (185 mm in diameter and 1.328 kg in weight), leading to a considerable obstruction of the urinary flow. The surgery was performed 9 weeks after the diagnosis due to difficulties making this procedure quickly available for patients in the Brazilian public health system.

Previous reports on giant bladder stones available on PubMed were assessed by searching for "giant" AND "bladder" OR "vesical" AND "stone" OR "calculus" OR "calculi" in article titles and abstracts, and 184 articles were found. This investigation was not able to find any description of a bladder stone with a larger diameter than that observed in the case reported here (185 mm). Regarding weight, four articles reported heavier bladder calculi than the stone found in the present case (1,328 g), weighting 1,815 g,[14] 1,640 g,[15] 1,620 g,[16] and 1,410 g.[17] No other urinary dysfunction was associated with the first case report,[15] whereas two of those bladder stones were associated with bladder carcinoma[15,17] and one of them was related to a neurogenic bladder.[16]

Various methods are available for the removal of bladder stones, including less invasive procedures such as cystolithotomy, extracorporeal shock wave lithotripsy, and transurethral cystolithotripsy.[11] Laparoscopic surgery is a good alternative, particularly in patients with solitary stones that are 3 cm or less.[18] Robotic cystolithotomy has also been performed in this context, with promising results.[19] However, the preferred procedure for the treatment of giant calculi is still the cystolithotomy, as observed in this case.

CONCLUSION

Here, the authors reported the urinary bladder stone with the largest diameter ever described. Giant vesical calculus is a rare but potentially life-threatening condition that can lead to symptoms that importantly impair the life quality of affected individuals. The available data on this disease are scarce, and this report describing such a huge calculus may contribute to a better understanding of this health problem.

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Bariatric Surgery and Risk of Urolithiasis: A Review

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Abstract

Obesity is a global epidemic for which dietary and lifestyle modifications alone are ineffective treatment strategies. Subsequently, more patients are opting for bariatric surgery, which has better success rates in weight loss and improvement of obesity-related comorbidities. These procedures involve anatomic alterations of the gastrointestinal tract resulting in either restriction of intake or malabsorption of nutrients. While obesity itself is an independent risk factor for urolithiasis, bariatric surgery may also adversely affect stone risk. Restrictive procedures appear to have the lowest risk, whereas malabsorptive procedures are associated with the highest risks of stone formation. Stone prevention strategies including dietary manipulation are critical in the management of the patients who have had bariatric surgery.

Key Points

1. Bariatric surgical techniques involve reconfiguration of the digestive tract to achieve weight loss by volume restriction, malabsorption, or a combination of both. Purely restrictive procedures are associated with a lower stone forming rates than malabsorptive procedures.

2. Obesity is associated with a lower urinary pH and increased excretion of oxalate, calcium, and uric acid, and decreased urinary citrate, which all predispose to urolithiasis.

3. Dietary modification in patients of postbariatric surgery is critical in the prevention of stones. These include maintaining a daily urine output of >2 L/day; decreased oxalate, fat, sodium and animal protein intake; and supplementation of vitamin D, calcium, and oral citrate.

INTRODUCTION

Obesity (BMI: >30 kg/m2) has reached epidemic proportions, both globally as well as locally in the Caribbean region, without discrimination against age, sex, race, socioeconomic, and educational levels.[1,2] More than one-third of the population in the USA and about one-half in Trinidad

and Tobago currently meet the definition of overweight or obese.[3-5]

Conservative methods such as diet and lifestyle modifications are often unsuccessful, or, at best, temporary with regards to sustainable weight loss.[3] The National Institutes of Health (NIH) consensus panel has established guidelines regarding which patients should be considered for bariatric surgery.[6] These recommendations include patients with BMI >40 kg/m2 or those with a BMI >35 kg/m2, with severe obesity-associated comorbidities.[6,7] Consequently, more patients are resorting to surgical options that have demonstrated superior success rates, not only in weight loss but also in the improvement of obesity-related comorbidities.[8] These reported successes have led to a six-fold increase in bariatric procedures in the USA alone over the past 10 years.[9,10] However, as these procedures become more popular, various ensuing metabolic derangements appear to increase the risk of urolithiasis.[3] The following discussion aims to highlight the delicate balance between the adverse effects of obesity and its treatment in the stone forming patient.

METHODOLOGY

A PubMed literature search on obesity, bariatric procedures, and risk of nephrolithiasis was completed and all relevant studies were selected and reviewed. Key search words included all variations of obesity, kidney stones, nephrolithiasis, restrictive bariatric procedures, malabsorptive bariatric procedures, laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), jejunoileal bypass (JIB),

Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion and duodenal switch (BPD-DS), hyperoxaluria, and hypocitraturia. Only articles written in English were selected. Review articles, original articles, case series, and international disease statistical databases were selected; however, news articles and commentaries were excluded. Institutional review board approval was not necessary as this is a review article and does not include any patient specific details.

BARIATRIC PROCEDURES

The bariatric era commenced in the early 1950s, when it was observed that sustained weight loss can be achieved by a surgically shortened small bowel with resultant secondary malabsorption.[11] Anatomical alterations of the gastrointestinal tract, either to restrict the quantity of food intake and/or to decrease the length of bowel through which absorption occurs, constitute the basis of bariatric surgery.[3] The techniques that are currently employed in weight loss surgery, based on these anatomical modifications, are classified as restrictive, malabsorptive or a combination of the two.[12]

Restrictive Procedures

Restrictive procedures include the gastric balloon, LAGB, and laparoscopic SG (LSG), with the latter being the most commonly performed restrictive procedure in recent times.[3] The gastric balloon is a relatively new short-term tool used in the fight against obesity and is primarily considered as a bridge to another procedure.[13] Laparoscopic adjustable gastric banding requires the placement of an inflatable silicone band around the proximal portion of the stomach thereby creating a gastric pouch of about 5–15 mL in capacity.[3] However, this procedure has lost popularity as it is less effective in achieving and sustaining weight loss compared with other bariatric procedures.[14] Nonetheless, LAGB is advantageous in several ways, including short operating time, minor changes to the gastrointestinal tract, and the opportunity to customise the degree of restriction based on individual needs.[15,16]

A SG involves removing approximately 80% of the stomach, with the remaining 'sleeve' extending from the gastro-oesophageal junction to the pylorus (Figure 1).[16] This procedure is associated with decreased production of the hormone ghrelin, which diminishes hunger and increases satiety.[17] LSG may serve as a first stage procedure for patients who may eventually require conversion to a RYGB, a procedure that may initially be impractical due to severe obesity.[3] However, over the past decade, the LSG has been considered a stand-alone operation for morbid obesity due to its encouraging early and midterm outcomes.[18,19] Additionally, this procedure appears to be favoured by many

bariatric surgeons due its technical simplicity and modest learning curve.[19]

Malabsorptive Procedures

Malabsorptive procedures achieve weight loss by decreasing the length of bowel exposed to food, thereby reducing the absorption of nutrients.[16] The JIB procedure was one of the first techniques pioneered with resultant severe malabsorption of both macro- and micronutrients.[20-22] However, due to life-threatening complications such as renal failure, hepatic encephalopathy, and high mortality rates, this procedure has since been abandoned in favour of safer alternatives.[20-22]

Combined Procedures

The evolution of malabsorptive procedures has led to combined malabsorptive and restrictive elements, with the RYGB being the most popular bariatric procedure in current times, accounting for about 80% of weight loss surgeries in the USA.[23] A 20–30 mL gastric pouch is created by stapling the proximal stomach and separating the distal portion (Figure 2).[24] The biliopancreatic limb is fashioned by dividing the small bowel about 50–150 cm distal to the ligament of Treitz, and a gastrojejunostomy is made between the gastric pouch and the distal separated limb of the small bowel (the Roux or alimentary limb).[24] The biliopancreatic channel is anastomosed to the Roux limb 150–300 cm distal to the gastrojejunostomy.[24] In addition to being extremely effective in achieving weight loss, altered gastric hormone secretion induced by this surgery encourages satiety and altered glucose metabolism, leading to significant improvement in the metabolic derangements of obesity.[3] However, abdominal cramps and nausea may occur because of 'dumping syndrome' as undigested food enters the small bowel.[25] This phenomenon may provide some therapeutic benefit as it may contribute to added weight loss by negative reinforcement of high calorie consumption.[3,25]

The BPD-DS, originally described by Scopinaro in 1979, also utilises a combination of malabsorptive and restrictive mechanisms (Figure 3).[26,27] It has documented efficacy in achieving and maintaining substantial weight loss in the population who are superobese (BMI: >50 kg/m2), with a randomised study demonstrating a 44.8% estimated body weight loss with BPD-DS compared with 31.2% following RYGB at 2 years follow-up.[28,29] The dumping syndrome is avoided in this pylorus-sparing procedure and, although weight loss efficacy is better than with RYGB, there is an increased risk of malnutrition related complications.[3]

Comparison of Restrictive and Malabsorptive Procedures

The urinary biochemical abnormalities seen in most patients who have had bariatric surgery are associated with an increased proclivity for urolithiasis. The exception is gastric banding, as shown in a study by Semins et al.[30] where, after 2 years of follow-up of their cohort, there was no increase in the risk of developing a stone or having a surgical intervention. The investigators postulated that the possible reason for this observation might be the significant weight loss experienced by the patients post-operatively, thereby reducing their risk for urolithiasis, since obesity by itself is an independent risk factor.[30] They also admitted that a follow-up of longer than 2 years may be warranted to further elucidate the relationship between gastric banding and stone risk.[30]

With respect to malabsorptive procedures, long-term follow-up revealed that up to 39% of patients post-JIB were found to have stones while those post-RYGB had doubled their risk of stone events.[3] In a retrospective study of patients undergoing RYGB, stone prevalence was noted to be increased by 70%, with 3.2% and 31.4% of post-operative patients developing de novo and recurrent stones, respectively.[31] These data clearly demonstrate the increased stone risk imposed by bariatric surgery for known stone forming patients, with resultant recommendations for post-operative evaluation for metabolic abnormalities and urolithiasis.[31]

OBESITY AND RISK OF NEPHROLITHIASIS

The association between increased BMI and risk of stone disease has been firmly established by various epidemiological studies, with patients who are obese having as much as a two-fold increased risk.[23,32] Obesity is associated with

several biochemical changes to the urinary milieu that pre-dispose to urolithiasis, including a lower urinary pH and increased urinary excretion of calcium, oxalate, and uric acid.[33] Additionally, urinary citrate, which is an important stone inhibitor, is found to be decreased in patients who are obese, a likely result of metabolic acidosis, which further potentiates the stone forming effect.[34] Metabolic syndrome, which collectively encompasses obesity, dyslipidaemia, insulin resistance, and hypertension, has also been linked to an increased risk of nephrolithiasis.[35,36] The plausible explanations include dietary factors, oxidative stress, inflammation, and insulin resistance, all of which may contribute to low urinary pH and subsequent development of uric acid stones.[35]

Dietary indulgences that are common among the population that is obese such as sweetened beverages, including soda and punches, which are associated with higher stone-forming rates.[37] On the other hand, a Dietary Approaches to Stop Hypertension (DASH)-style diet has been shown to decrease kidney stone incidence due to the high vegetable and fruit, moderate low-fat dairy, and low animal protein intake.[37] These favourable effects seen with the DASH diet are a result of increases in urine volume, pH, and urinary excretion of citrate, potassium, magnesium, sulphate, and phosphate.[33] Another potential pathogenic mechanism for stone formation in patients who are obese is increased intestinal absorption of oxalates resulting from a reduction in intestinal colonisation by the oxalate-degrading microorganism, Oxalobacter formigenes.[38]

BARIATRIC PROCEDURES AND RISK OF NEPHROLITHIASIS

Although obesity-related complications may be reversed by bariatric surgery, the evidence is mounting that these interventions may also adversely impact stone risk.[3] Each type of surgery is accompanied by varying levels of stone risk (Table 1), with restrictive procedures associated with the least risks approaching that of nonoperative controls, RYGB intermediate risk (7.65–13%) and malabsorptive with the greatest risk (22.0–28.7%).[39,40,42-44] There are various complex underlying pathophysiologic mechanisms associated with nephrolithiasis following bariatric surgery, including low urine volume, aciduria, hyperoxaluria, and hypocitraturia.[42,45] Various studies have demonstrated that malabsorptive procedures have well documented urinary metabolic derangements, with some types of surgeries such as JIB and RYGB resulting in hyperoxaluria in about 50% of patients. Conversely, restrictive procedures such as gastric banding do not appear to have this problem.[39]

Urine Volume and pH

A decreased urine volume is common following bariatric procedures due to restricted gastric volumes and is one of the chief causes of urinary crystallisation and stone formation.[42] Many studies have consistently documented a reduction in 24-hour urine volume in bariatric surgery patients from pre-surgery to post-surgery, with the majority of patients maintaining persistently low urine volumes thereafter.[42] Acidic urine (pH: <4.6) has been demonstrated in several series of patients following RYGB, leading to supersaturation of uric acid and formation of uric acid stones.[42,45] However, even in the presence of aciduria, the occurrence of uric acid stones is still less frequent than calcium oxalate stones following bariatric surgery.[42]

Hyperoxaluria

The increased incidence of urolithiasis following bariatric surgery is probably multifactorial, with the likely culprits being fat malabsorption, increased oxalate absorption and altered gut microflora.[46] Fat malabsorption, which occurs predominantly in malabsorptive procedures, leads to enteric hyperoxaluria as fatty acids undergo saponification with intestinal calcium. This leaves behind increased intestinal quantities of unbound oxalates with subsequent colonic absorption and secretion into the urine.[47,48] In a study by Nelson et al.,[49] 21 of their 23 patients presented with a symptomatic stone resulting from enteric hyperoxaluria following RYGB.[48] Furthermore, several studies have implied that patients undergoing RYGB are at higher risk for nephrolithiasis post-surgery than pre-surgery.[26,50,51-53] An even greater concern was the occurrence of oxalate nephropathy and renal failure in a small subset of patients, an additional consideration for those with high urinary oxalate excretion.[49]

Moreover, malabsorptive bariatric procedures are associated with alterations in gut microbial flora, particularly decreased colonisation with O. formigenes, an anaerobic commensal species of bacteria present in the human colon.[54] These organisms utilise oxalates as their sole energy source and decreased colonisation results in augmented oxalate absorption, hyperoxaluria, and recurrent calcium oxalate stone disease.[42,54] Conversely, while restrictive bariatric procedures may provoke specific metabolic derangements, they are not associated with hyperoxaluria since a malabsorptive state is not induced.[3] However, there may still be a negative impact on stone risk as a consequence of a restricted gastric volume and an overall decreased oral intake of fluids, calcium, magnesium, and citrate containing foods.[3]

Hypocitraturia

Citrate, a critical inhibitor of crystallisation, forms soluble complexes with calcium in the renal tubules, thereby reducing urinary supersaturation and subsequently, calcium oxalate and calcium phosphate precipitation.[42] Hypocitraturia, defined as urinary citrate levels <320 mg/day, is associated with an increased risk of urolithiasis. This metabolic derangement is commonly observed in acidotic states as renal citrate reabsorption increases and urinary citrate excretion is reduced.[45,55] Penniston et al.[48] after evaluating post-operative 24-hour urine specimens, have demonstrated that patients who have had RYGB have higher urinary oxalate and lower urinary citrate levels when compared to gastric banding patients.[8] While urine volume was low in both groups, it was postulated that the observed hypocitraturia in the patients who have had RYGB was a result of increased bicarbonate losses from the gastrointestinal tract.[48]

MANAGEMENT OF STONE RISK IN PATIENTS OF POST-BARIATRIC SURGERY

While available data indicate that bariatric procedures are associated with an increased stone forming risk, the presence of hyperoxaluria or previous stone disease are not contraindications for bariatric surgery.[3] Extensive pre-operative patient counselling is, therefore, prudent, in addition to 24-hour urine evaluations prior to RYGB, especially in the setting of known stone disease.[3] Additionally, monitoring of renal function, renal tract imaging, and appropriate dietary advice should be encouraged in the follow-up of these patients.[56]

Stone prevention therapy in patients of bariatric surgery is critical, with dietary modifications being the most important component of this strategy.[3] Maintenance of daily urine output of >2 L/day is essential and fluid intake in the form of frequent small quantities is advisable, as some procedures may be prohibitive of large volume intake.[3,23] Other key elements of dietary modification include decreased oxalate

(<100 mg/day) and fat intake to minimise enteric absorption of oxalates.[55] Elevated levels of fatty acids reaching the distal intestines due to surgical redirecting of food in patients of bariatric surgery will chelate calcium, enabling the absorption of free oxalate and resultant hyperoxaluria.[56] Reduced sodium and animal protein intake are advised. Additionally, supplementation of vitamin D and calcium should be considered, with the recommended daily calcium intake of 1,000–1,200 mg/day being instituted early in the post-operative period.[57] Supplemental calcium binds and enhances oxalate excretion, so its intake should be timed to correspond with oxalate consumption. Oral citrate salts such as calcium or potassium citrate can be used to correct metabolic acidosis and hypocitraturia.[55]

The oral administration of O. formigenes or its oxalate degrading enzymes is being investigated in patients with primary hyperoxaluria with the aim of increasing colonic oxalate metabolism, thereby decreasing systemic absorption.[26] While further studies regarding this strategy are required, this option may also prove useful in patients with bariatric hyperoxaluria.[3]

CONCLUSION

Obesity is a well-known risk factor for urolithiasis but, on the other hand, its management by some forms of bariatric surgery is associated with an exacerbation of this risk. However, there is a definite role for bariatric surgical interventions in the management of obesity and its multitude of

related comorbidities. Current available literature appears to concur that a purely restrictive procedure such as gastric banding is associated with a much lower stone forming rate than malabsorptive procedures. The biochemical changes induced by bariatric surgery, particularly hyperoxaluria and hypocitraturia, are intricately linked to nephrolithiasis. It is hoped that a better understanding of their underlying pathophysiology may help to prevent or modify the risk of kidney stones in this population. Fortunately, the multifactorial nature of bariatric surgery-associated lithogenicity lends itself well to a broad spectrum of prophylactic approaches, which have demonstrable efficacy in preventing oxalate nephrolithiasis and downstream chronic renal impairment.

Take Home Points

Bariatric surgical techniques involve reconfiguration of the digestive tract to achieve weight loss by volume restriction, malabsorption, or a combination of both. Purely restrictive procedures are associated with a lower stone forming rates than malabsorptive procedures.

Obesity is associated with a lower urinary pH and increased excretion of oxalate, calcium, and uric acid, and decreased urinary citrate, which all predispose to urolithiasis.

Hyperoxaluria, which occurs more commonly in malabsorptive bariatric procedures, are due to fat malabsorption, increased oxalate absorption and altered gut microflora.

Hypocitraturia (urinary citrate level: <320 mg/day) frequently occurs in certain malabsorptive procedures such as RYGB.

Bariatric procedures are not contraindicated in the presence of hyperoxaluria or previous stone disease.

Dietary modification in patients of post-bariatric surgery is critical in the prevention of stones. These include maintaining a daily urine output of >2 L/day; decreased oxalate, fat, sodium and animal protein intake; and supplementation of vitamin D, calcium, and oral citrate.

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Holmium Laser Removal of Antegrade-Placed Ureteral Stent Suture via Ureteroscopy

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Abstract

Antegrade conversion to nephroureteral stent is common after percutaneous nephrostomy tube placement for obstruction when retrograde alternatives fail. Nephroureteral stents often have a nylon retaining suture attached to aid in placement and removal. If the nephroureteral suture is not removed, it can become embedded in the renal parenchyma as nylon is unabsorbable, preventing stent removal and potentially leading to adverse outcomes. This case report describes a complication of antegrade nephroureteral stenting and shows that retrograde ureteroscopy with holmium lasering of the retained suture was an effective treatment for the removal of retained stents. Furthermore, after a difficult extraction of the nephroureteral stent, the patient displayed minimal post-operative sequelae, and no visible defects on follow-up renoscopy.

Learning Points

1. When retrograde alternatives fail following percutaneous nephrostomy tube placement for obstruction, it is common practice to use a nephroureteral stent. However, this poses potential problems, including prevention of removal of the stent if the attached non-absorbable nylon suture is not removed, with possible adverse sequelae.

2. Prior to this case study, no literature existed on the rare phenomenon of stent suture tethering to the renal parenchyma and how this prevents removal.

3. In this case, retrograde ureteroscopy with holmium laser on the retained suture proved an effective treatment in the removal of the stent.

INTRODUCTION

Ureteral obstruction can be caused by malignancy, urolithiasis, external compression, congenital defects, and iatrogenic injuries.[1] Subsequent hydronephrosis secondary to obstruction is often decompressed by antegrade or retrograde access.[2] Retrograde access is often performed via cystoscopy with the placement of a nephroureteral stent, whereas antegrade access is typically performed with a percutaneous nephrostomy catheter, percutaneous nephroureteral tube, or percutaneous antegrade ureteral stent.[3] The interventions are performed under fluoroscopy to ensure correct positioning. Ureteral stents are associated with multiple complications including stent migration, urinary tract infection (UTI), encrustation, and occlusion.[4] Increased stent indwelling time, typically longer than 6 weeks, is one factor responsible for multiple of these aforementioned complications.[5]

Nephroureteral stents are often manufactured with a permanent suture at the distal end to facilitate placement and subsequent extraction of the stent.[6] Previous studies have shown no change in complications such as UTI or post-operative morbidity in patients with existing ureteral stent extraction strings.[7] Similarly, extraction strings have comparable rates of adverse events.[8] However, no current literature exists to show that the stent suture can tether to the renal parenchyma to prevent removal. This article presents a case of a patient with a retained suture in the renal papilla from antegrade ureteric stent placement, with the objective of demonstrating that retained string may ultimately lead to tethering and other complications.

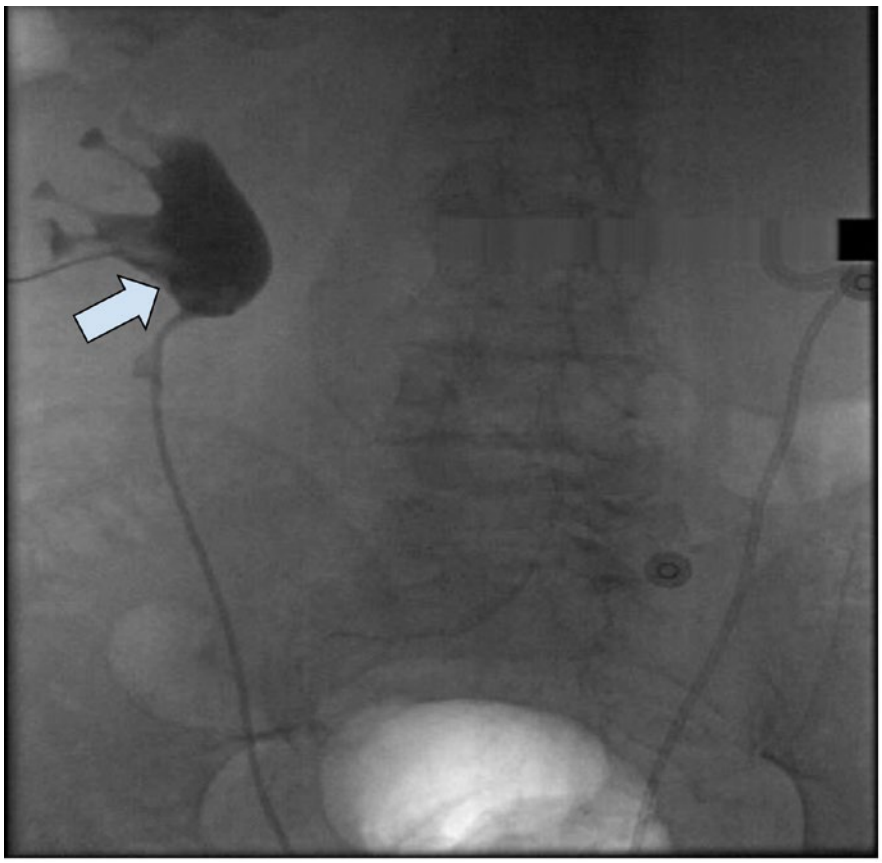
CASE PRESENTATION

A 95-year-old male with hypertension and end-stage renal disease on haemodialysis (HD) for 7 months initially presented for bilateral nephroureteral stent removal. The patient had a history of congenital, bilateral ureteropelvic junction obstructions, first diagnosed 6 years prior to initial presentation. The ureteropelvic junction obstructions were managed with bilateral nephroureteral stents in an effort to maintain his kidney function. The patient was currently being treated for a UTI with urine cultures positive for *Enterococcus* and *Pseudomonas*. He had undergone multiple routine nephroureteral stent exchanges prior to initiating HD; however, once starting HD, the removed left nephroureteral stent was unable to be replaced due to loss of retrograde access intraoperatively. Therefore, interventional radiology placed a left percutaneous nephrostomy catheter, which was internalised to an 8 Fr, 26 cm double-J stent 3 days later (Figure 1). The patient was ultimately discharged post-nephroureteral stent insertion.

The patient presented to the hospital 7 months later for bilateral ureteric stent removal due to minimal urine production on HD and concerns for potential nidus for infection with indwelling stents. The patient was ultimately taken to the operating room for stent removal. Intraoperative plain radiography and fluoroscopy confirmed no malpositioning or encrustation of bilateral stents.

The right ureteric stent was successfully removed with flexible graspers. However, when attempting to remove the left stent, the stent was seemingly fixed in position at the proximal portion. The distal end was mobilised to the meatus and a guidewire was then used to attempt to straighten the stent to aid in movement, but it did not change position despite no retaining curl seen. A retrograde ureteroscopy, performed with a 7.4 Fr flexible ureteroscope with a 3.6 Fr working channel, alongside the stent showed a blue suture preventing the stent from being removed. A 200 micron holmium laser fibre (SlimLine™, Boston Scientific, Massachusetts, USA) was required to cut the proximal part of the suture and allow the stent to be extracted. Renoscopy was then performed and identified a suture attached to a papilla in the lower pole, revealing the source of stent immobility. This suture was unable to be removed with ureteroscopic graspers as it was firmly embedded within the renal pelvic wall. The holmium laser was utilised again to cut directly on the papilla and remove pieces of the suture with the ureteroscopic graspers. The proximal remaining portion of the suture was left in the parenchyma since it was unable to be removed without damaging the parenchyma (Figure 2). Gross appearance of the suture can be seen in Figure 3.

Figure 1: Fluoroscopy with posterior-anterior radiograph of left antegrade ureteric stent position performed by interventional radiology (arrow).



A new left double-J stent nephroureteral stent was placed, as the patient elected to undergo double-J stent exchanges instead of definitive surgical therapy, such as pyeloplasty. On repeat renoscopy 3 weeks later, there were no defects seen in the renal papilla and the nephroureteral stent was removed. On a 10-month follow-up, the patient was continued on HD and has had no additional UTIs, flank pain, or repeat urologic interventions.

DISCUSSION

Nephroureteral stents are frequently used in patients with ureteral obstruction, obstructed pyelonephritis, and post-surgical treatment of urolithiasis.[9] Manufacturers often produce the stents with a string attached, making these stents manageable to remove or reposition.[10] These strings are made of fine suture material, commonly composed of nylon.[11] Nylon is a nonabsorbable suture, which can lead to potential complications if not removed. Multiple studies have found no differences in quality of life or post-operative complications in patients with retained ureteral stent extraction strings.[7,12] However, as the authors' case has demonstrated, complications can arise with these extraction strings if left *in situ*. Additionally, hypercalcaemia is a common sequelae of end-stage renal disease and may have precipitated stent encrustation via dystrophic calcification, furthering risk for stent complications and difficult removal.[13]

There was no reported difficulty in placement, per the procedural note, and no skin defect. The incidence of this occurrence is unknown, and no known case reports have outlined the removal of retained suture within the kidney using a holmium laser. Other stent complications, including proximal stent knotting, have been successfully treated with holmium laser ablation.[14,15] In both cases, the laser was used to transect the

Figure 2: Ureteroscopy displaying residual suture (arrow) present in renal parenchyma after holmium ablation and stent removal.

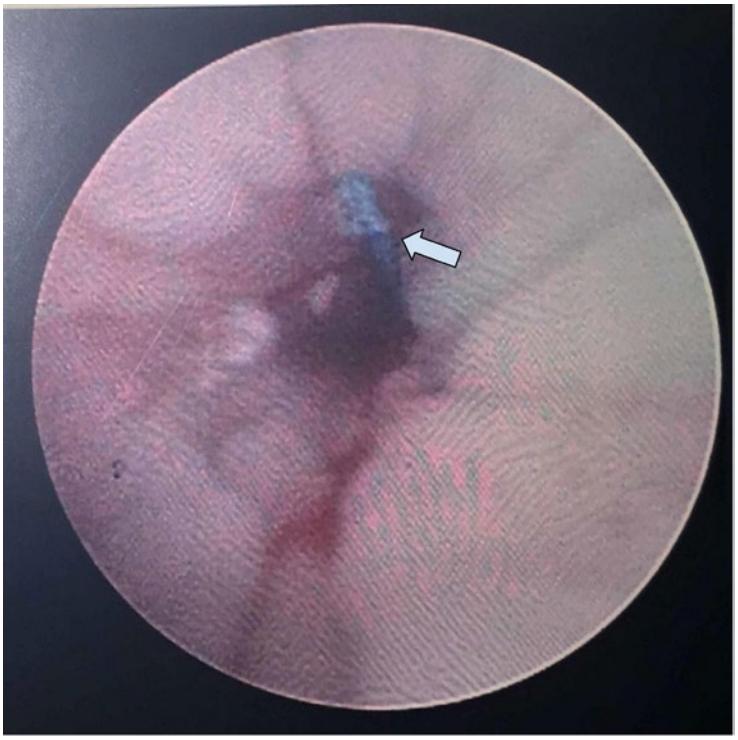
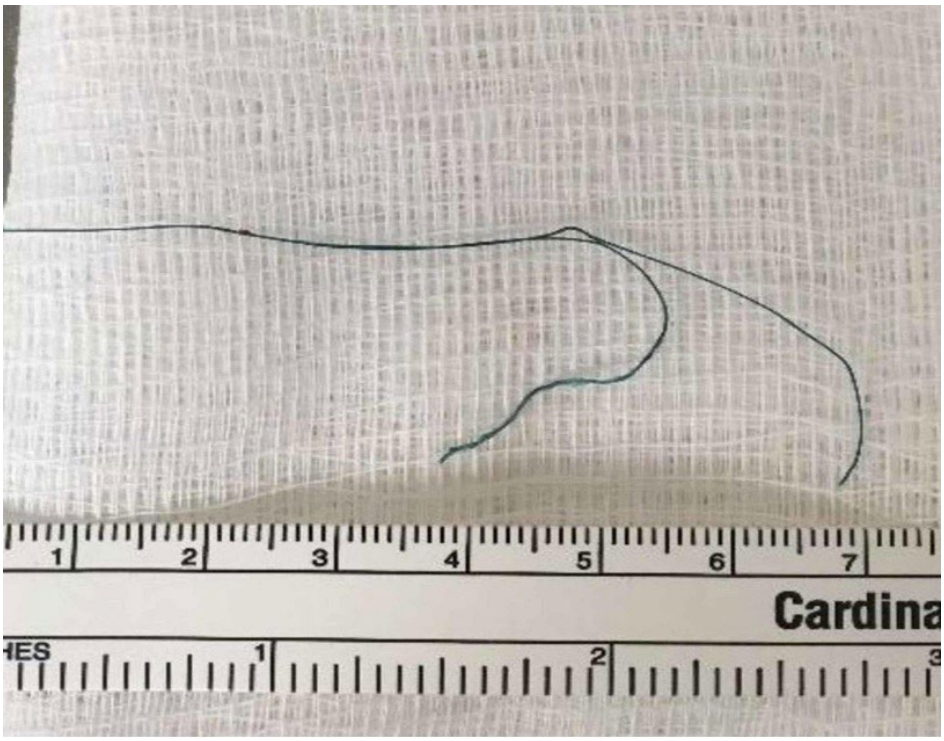


Figure 3: Gross suture specimen after ureteroscopic removal.



proximal knot, resulting in detachment. In this case, the suture was unable to be pulled with graspers, but laser ablation on dusting settings appeared to remove nearly all components in the collecting system despite leaving behind a short segment in the renal parenchyma. Current literature defines optimal dusting settings for retrograde ureteroscopy when using a 120 watt holmium laser (Lumenis®, Pulse™, Boston Scientific, Massachusetts, USA) in the renal collecting system as 0.2 to 0.3×70; JxHz.[16]

Foreign bodies can become a nidus for stones, fistulas, and infection;[17] at 10-month follow-up post-stent removal, the patient had an uncomplicated recovery with stable follow-up. There was no defect seen on repeat renoscopy and, since there is an increased rate of complications with retained suture in the renal parenchyma, imaging will be performed annually, or earlier if the patient becomes symptomatic.

Attempted removal of defective ureteral stents without proper caution and management carries a risk of injury. Failure to remove the permanent suture on the nephroureteral stent prior to deployment can cause stent retainment. This case shows that a holmium laser can be an effective method to incise the suture.

CONCLUSION

Retained suture from an antegrade ureteric stent appears to be a rare phenomenon preventing cystoscopic stent removal. Given the case, the authors recommend caution when using a suture-dwelling stent during an antegrade approach. Retrograde ureteroscopy with holmium lasering of the retained suture appears safe for stent removal with tethering suture in the renal parenchyma and can avoid injury to the collecting system.

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