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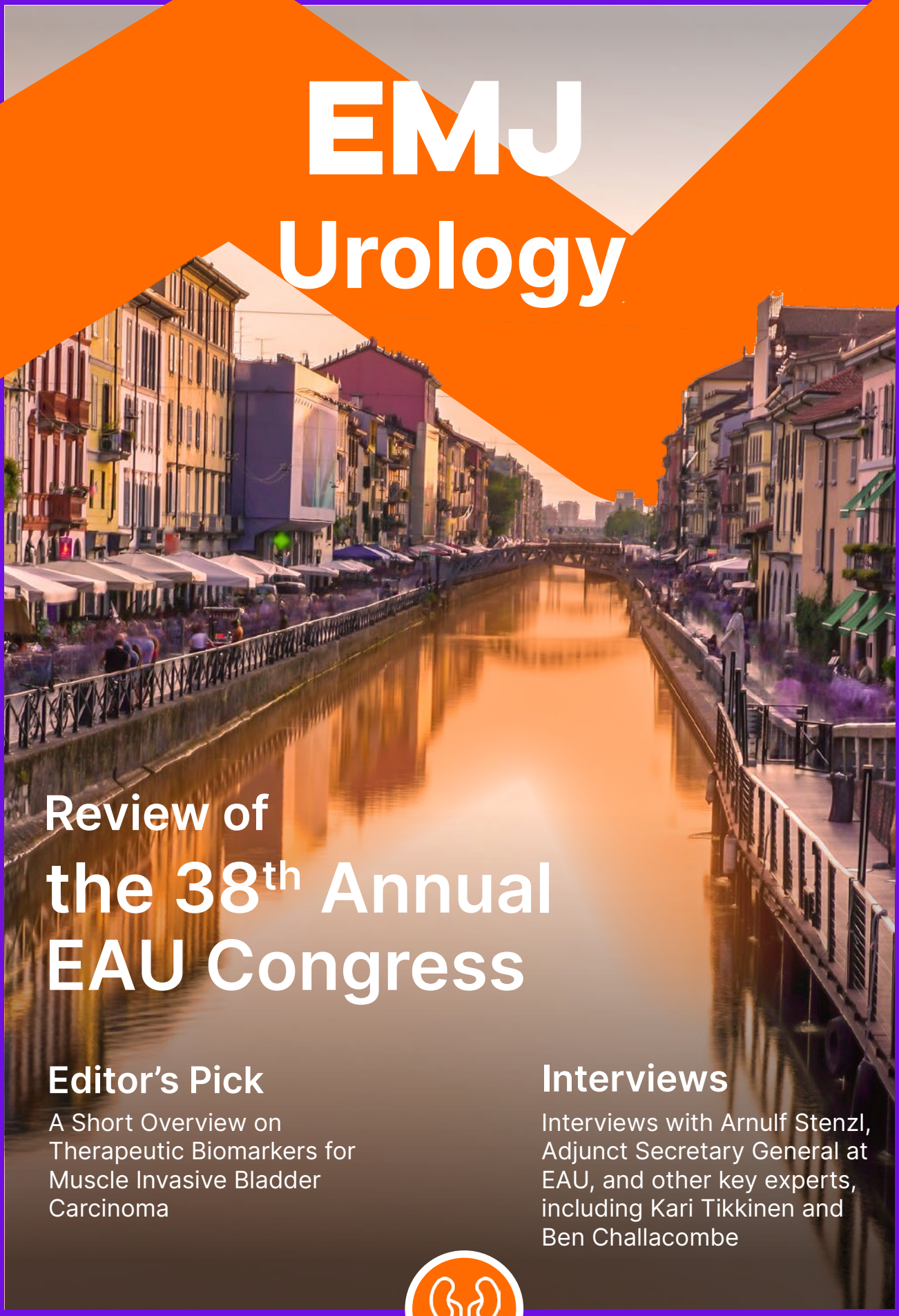

Review of the 38th Annual EAU Congress

Editor's Pick

A Short Overview on Therapeutic Biomarkers for Muscle Invasive Bladder Carcinoma

Interviews

Interviews with Arnulf Stenzl, Adjunct Secretary General at EAU, and other key experts, including Kari Tikkinen and Ben Challacombe

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Aims and Scope

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

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

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the 2023 issue of *EMJ Urology*, covering the European Association of Urology (EAU) 2023 Congress, which this year took place in Milan, Italy. As always, our team was present at the event, and we are proud to bring you the key updates and report on key discussions.

Of particular interest were the presentations around the recommendations for prostate cancer screening in Europe, which discussed how these could be implemented across European countries and how overdiagnosis could be reduced. This issue also covers an interesting debate around the use of robotic surgery versus open approach for ileal conduit formation.

EMJ Urology also features a number of engaging interviews with key opinion leaders who discuss artificial intelligence in urological surgery, biomarkers of urothelial carcinoma, and the most cutting edge surgical techniques. Through their insights and innovative approaches there is a lot to be learnt regarding future directions in urology and areas of potential focus.

Our Editor's Pick for this issue focuses on the molecular pathways and therapeutic biomarkers for urothelial bladder cancer. The issue also contains an interesting case report of unexplained renal impairment in a patient with seminoma.

I would like to close this by thanking our authors, reviewers, and our Editorial Board for their contribution in bringing this issue together. I hope you enjoy this content!

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Foreword

Dear Colleagues,

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

In this edition, we have a number of very interesting papers, including my Editor's Pick. My choice is a review on bladder cancer genetics, focusing on molecular changes and their significance in pathogenesis and progression of urothelial carcinoma. Also included are insightful abstracts, features, and interviews with key opinion leaders.

This issue includes a review of the 38th European Association of Urology (EAU) Congress in Milan, Italy, the largest urology meeting in Europe and an event organised every year, attracting a great deal of attention worldwide. EAU23 involved many sessions, debates, presentations, and courses on urology, which discussed and presented the latest developments and cutting-edge science. I remember the virtual EAU Congress held in July 2021, due to the COVID-19 pandemic, and it was great to meet colleagues again in person in Milan. Based not far from the beautiful area of Lake Como, it was a very attractive setting for a meeting.

I would like to take this opportunity to thank everyone who helped bring this issue together. I hope you enjoy reading and invite you all to submit your work to *EMJ Urology*.

Kind regards,

A. Erdem Canda

Professor of Urology, Koç University School of Medicine, Department of Urology, İstanbul, Türkiye

EAU 2023

Review of the 38th Annual Meeting of the European Association of Urology (EAU) 2023

Location:	Milan, Italy
Date:	10th-13th March 2023
Citation:	EMJ Urol. 2023; DOI/10.33590/emjurol/10306612. https://doi.org/10.33590/emjurol/10306612.

WELCOMED by the graceful vocals of the Italian Tenors, Christopher Chapple, European Association of Urology (EAU) Secretary General, opened what he described as a "vibrant programme" at the 38th Annual EAU Congress, held in Milan, Italy between the 10th-13th March 2023. Boasting a rich history of art, architecture, and culture, and home to Leonardo da Vinci's famous mural 'The Last Supper', over this weekend Milan traded its role as a global hub for fashion and design to host the largest urology event in Europe.

> **"I know the Assocation is in very strong hands."**

Returning to Italy after successful meetings there in 2008 and 2013, EAU23 offered the chance for key opinion leaders to convene and share their expertise. In this special year, celebrating the 50th anniversary of the EAU, the congress aimed to enrich patient care by allowing experts to participate in live surgeries, case discussions, debates, and other insightful presentations which comprised the scientific programme.

A total of 9,219 on-site registrations and 581 virtual registrations brought combined participation to an impressive figure, close to ten thousand. Over 4,500 abstracts were submitted, and the top tier of these were presented over the course of the 4-day event, found alongside an insightful selection of urological guideline updates, and game-changing plenary sessions.

During the General Assembly, having worked within the EAU for 30 years, and after an 8 year period of leadership, an emotional Chapple handed his Secretary General's medal over to his successor, Arnulf Stenzl, EAU Adjunct Secretary-General, with the statement, "I know the Assocation is in very strong hands." He sincerely thanked his colleagues for all of their contributions, and the tireless support he received in his many years of service. Chapple's successor, Stenzl, stated: "I am proud to be able to serve this great organisation, and am looking forward to stepping into some large shoes."

Several new EAU Honorary Members were welcomed; Allen Chiu, Yang-Ming University, Taiwan; Christopher Evans, University of California, USA; Helmut Haas, University of Mainz, Germany; Alejandro Rodríguez, Wake Forest University School of Medicine, North Carolina, USA; Monique Roobol, Erasmus University Medical Centre, Rotterdam, the Netherlands; and Alexandre de la Taille, Assistance Publique–Hôpitaux de Paris, France. The prestigious Willy Gregoir Medal, for significant contribution to the development of the urological specialty in Europe, was awarded to Luis Martínez-Piñeiro, La Paz University Hospital, Madrid, Spain. James Catto, University of Sheffield, UK, received the Frans Debruyne Life Time Achievement Award for longstanding

and important contributions to the activities and development of the EAU.

Each year, the best European paper published on minimally-invasive surgery in urology is awarded the Hans Marberger Award. The 2023 recipient was Riccardo Campi, Careggi University Hospital, Florence, Italy. The Innovators in Urology Award is not given annually, but recognises inventions and clinical contributions that have had a major impact on influencing the treatment and/or diagnosis of urological disease. This was given to Peter Wiklund, Karolinska University Hospital, Sweden. A new award was also granted in the form of the Ernest Desnos Prize for extraordinary contributions to the field of urological history, and this was presented to Remigio Vela Navarrete, Universidad Autónoma de Madrid, Spain. Milan local Eugenio Ventimiglia, San Raffaele Hospital, Milan, Italy, received the Prostate Cancer Research Award for the best paper published on clinical or experimental studies relating to prostate cancer, and Rachel Giles, Van Hall Larenstein University of Applied Sciences, the Netherlands, received the first ever Patient Advocacy Medal of Excellence for effective advocacy and a positive impact on European urology. The Crystal Matula Award for a young, promising European urologist went to Juan Gómez Rivas, Universidad Complutense de Madrid, Spain; you can find an insightful interview with Gómez Rivas later in this issue.

Peter Albers, the new Chair of the EAU Scientific Congress Office, brought the weekend to a close at the 'Best of EAU23' session of take-home messages. In his final remarks, he thanked delegates for their attendance, and outlined plans for the EAU24 congress, to be held in Paris, France, in April 2024.

This issue of *EMJ Urology* contains our scientific highlights from the 38th Annual Meeting and 50th anniversary of the EAU, and an interview with the new Secretary General, Arnulf Stenzl. Included in this review of the congress is a selection of the cutting-edge press releases shared, on topics such as digital rectal examination and active monitoring of prostate cancer, genetic testing of urine for bladder cancer, and an update to the safety profile of vasectomies.

"I am proud to be able to serve this great organisation, and am looking forward to stepping into some large shoes."

Do Patients Prefer Male or Female Urologists?

PREFERENCE of the gender of a urologist depends on the patient's condition, according to data presented at EAU23. While the field involves very intimate conditions, patients do not always prefer to be treated by someone of the same gender. Patients with painful conditions, for example, prefer to be treated by a female doctor.

Researchers from the University of Munich, Germany, created a survey to look at whether patients associate certain skills to a gender, and how their choice would change depending on the situation or their symptoms. In total, 1,012 patients who visited the hospital during 2021 filled out the questionnaire. Of those, approximately three-quarters were male, just under one-quarter were female, and three patients were non-binary. The cohort included all ages and educational and economic backgrounds.

Patients were asked about the impact of their conditions on their lives, and whether they thought a male or female urologist would understand them best. Two-thirds of participants expressed a preference for the gender of their urologist in at least one scenario. While they would usually prefer a urologist of their own gender, in certain situations this was not the case. All patients expressed that they would prefer a male urologist for conditions that were embarrassing, caused them concern or inconvenience, or limited their daily activities. For painful symptoms, however, both male and female patients would prefer a female urologist.

Regarding consultations and surgery, one-third of patients expressed a preference, with a 60:40 split in favour of a male urologist when it came to consultations, and an 80:20 split for operations. Male patients believed male urologists would have more practical skills, while females thought a female urologist would be more empathic. Both genders stated that a urologist of their own gender would be easier to talk to, and would understand their body better.

Researchers concluded that there is a need for a more equal mix of male and female clinicians, as urology remains a male-dominated field. Lead researcher Alexander Tamalunas, University Hospital Munich, stated: "Patients will already find it hard to speak openly to urologists about these conditions, and this may be exacerbated by cultural sensitivities in some communities. It's vitally important that any additional barriers which we can control, such as the gender of the consultant, are removed, and for that we need to encourage and support more women in the profession." ●

"Male patients believed male urologists would have more practical skills, while females thought a female urologist would be more empathic."

UK Study Claims That Vasectomies Are Even Safer Than Reported

VASECTOMIES are much less likely to lead to complications than expected, claims a novel UK study from researchers at the Gloucestershire Hospitals NHS Foundation Trust, where outcomes from over 90,000 vasectomies performed over 15 years were reviewed. Presenting at the EAU23 Congress in Milan, Italy, researchers suggested that the existing leaflets which describe the potential complications to patients are established on obsolete data.

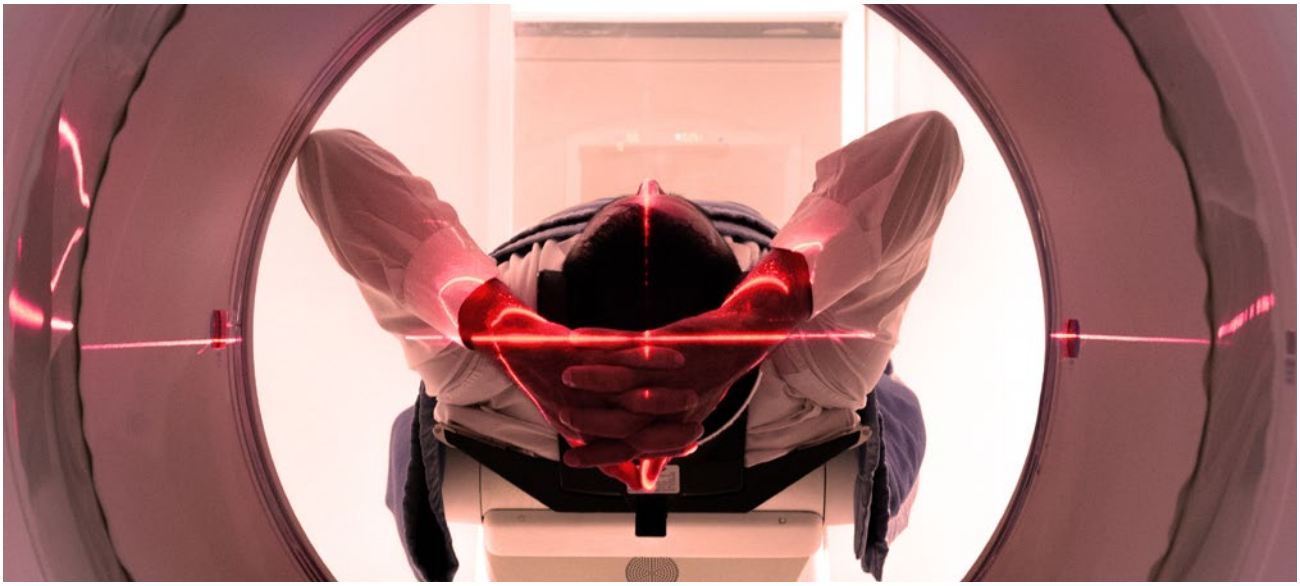
> **"These figures might encourage more men to undergo the procedure."**

In the UK, approximately 11,000 vasectomy operations are performed annually, with the majority being operated in primary care settings by specialist general practitioners. The Association of Surgeons of Primary Care, headed by Gareth James, collected data from 94,082 vasectomies between 2006–2021, mostly through patient questionnaires. Patients were asked to complete a questionnaire on the day of their surgery, and were asked to report any problems 4 months post-operation.

Julian Peacock, who led the review alongside John Henderson, both of the Gloucestershire Hospitals NHS Foundation Trust, stated: "This large dataset had never been independently analysed, and doing so has enabled us to update the standard complication rates, some of which dated back to the 1980s."

Researchers reported that approximately 0.12% of patients experienced chronic scrotal pain, one of the most significant complications of a vasectomy. This figure is relatively low compared to the 'up to 5%' quoted by the British Association of Urological Surgeons (BAUS) patient information leaflet about vasectomies. The team emphasised how patients can be deterred by the chances of chronic scrotal pain, especially as it is a difficult condition to manage. They expressed the importance of up-to-date data, and how it provides a more coherent understanding of the chances of complications arising. Likewise, the rates of infection requiring antibiotics are quoted as 2–10% in the BAUS statistics, but the researchers found this was closer to 1.3%.

The authors emphasised that vasectomies are a very reliable and safe contraception method. Peacock stated: "These figures might encourage more men to undergo the procedure, so we hope our research will be incorporated in the guidelines that provide information for pre-vasectomy counselling and leaflets." ●



Early-Stage Prostate Cancer Screening: Is Digital Rectal Examination Effective?

FINDINGS from the PROBASE multicentre prostate cancer screening study, presented at EAU 2023 in Milan, Italy, on 12th March, reveal that digital rectal examination (DRE) is less effective in identifying early-stage prostate cancer than other detection methods, such as serum prostate specific antigen (PSA) testing.

The PROBASE trial, co-ordinated at the German Cancer Research Center (Deutsches Krebsforschungszentrum [DKFZ]), Heidelberg, Germany, enrolled 46,495 males aged 45 years between 2014–2019, across four university sites in Germany. The two arms of the trial were those who were offered serum PSA testing at 45 years of age, and those offered DRE with delayed PSA testing at 50 years of age.

Of those in the DRE and delayed PSA testing arm, 6,537 patients had a DRE performed. Referral for a follow-up biopsy secondary to suspicious examination findings occurred in 57 patients, and three were subsequently diagnosed with prostate cancer. The detection rate using DRE was much lower than the detection rate using serum PSA testing, with lead study author, Agne Krilaviciute, Division of Personalized Early Detection of Prostate Cancer, DKFZ, highlighting: "PSA testing at the age of 45 detected four-times more prostate cancers."

The findings imply that DRE as a prostate cancer screening method lacks the sensitivity to detect early-stage disease, which is the main reason for screening. The researchers postulate that this could be explained by tissue changes in early-stage prostate cancer being too subtle to pick up on DRE. The authors further noted, in a separate analysis where MRI scans were performed prior to biopsy, 80% of prostate cancers were located in areas that should be within reach on DRE. However, this was not reflected in the trial findings, which yielded a negative result in 99% of cases.

> **"DRE as a prostate cancer screening method lacks the sensitivity to detect early-stage."**

Moreover, the team suggested that the examination itself may contribute to the low prostate cancer screening participation rate in Germany, and stated that more patients may take up screening if offered serum PSA testing instead.

As a result of the study findings, the researchers are advocating that serum PSA testing and MRI scanning should replace DRE in prostate cancer screening programmes. ●

Advanced Imaging May Aid Diagnosis and Treatment of Prostate Cancer

PROSTATE-SPECIFIC membrane antigen (PSMA) PET-CT, an advanced imaging method, could aid the diagnosis of prostate cancer by providing a clearer view of suspected tumours during biopsy, and helping clinicians target where to take samples, according to data from the University Hospital Bonn, Germany, presented at EAU23 in Milan. The technique may help clinicians to make better decisions about subsequent treatments.

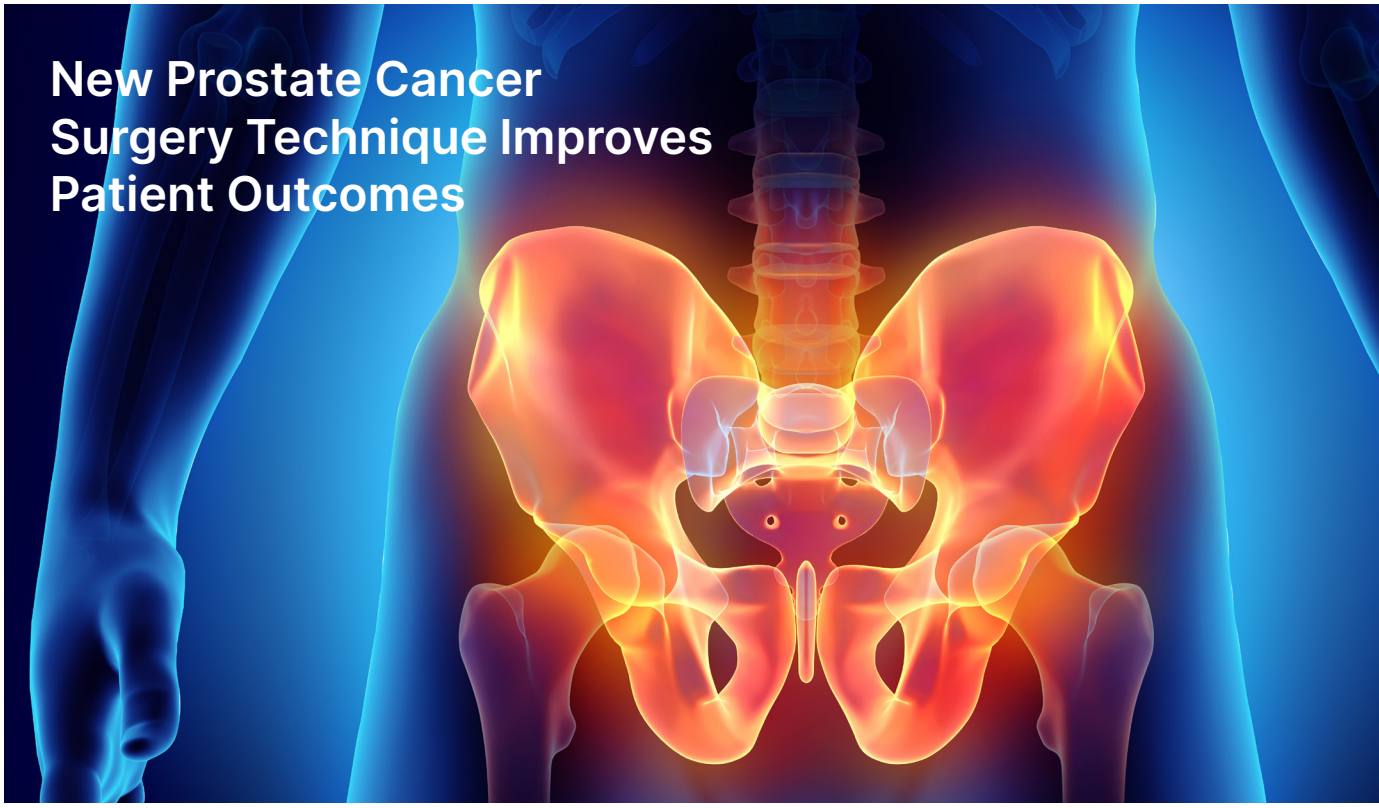
> **"It appears to be having an impact in high-risk patients."**

The DEPROMP trial included approximately 200 males who underwent MRI, PSMA-PET-CT, and biopsy; however, researchers hope to have more than 230 patients enrolled by the end of the trial. Two separate teams of urologists randomly looked at the scans, with one group only seeing the results of the MRI and biopsy without the PSMA-PET-CT data, while the other group was given all the results. The researchers analysed and compared the treatments chosen by the two teams based on the information they were given. They noted that adding the PSMA-PET-CT caused clinicians to change how they would treat patients with clinically significant prostate cancer in 19% of cases, compared to the standard scans. Furthermore, this method helped clinicians detect significantly more significant prostate cancers.

> **"The question we are considering is whether the additional diagnostics are worthwhile."**

Study lead Philipp Krausewitz, University Hospital Bonn, stated: "It appears to be having an impact in high-risk patients, but we also saw false positives in 6% of patients that meant we needed further investigations. The question we are considering is whether the additional diagnostics are worthwhile." They explained that clinicians might perform surgery to remove the cancer or give the patient chemotherapy, while it is not clear yet how these decisions will affect patient outcomes. As it is an expensive technique that is not available everywhere, more research is needed to understand how the method can be used effectively, and substantial improvement in diagnostic capability will need to be proven to be cost-effective. However, in the meantime, the technique can be used for selected challenging diagnostic cases, and cases where an MRI cannot be performed.

New Prostate Cancer Surgery Technique Improves Patient Outcomes



LYMPHATIC fluid collecting in the pelvis is one of the most common post-operative complications following robot-assisted keyhole surgery for prostate cancer, affecting around 10% of patients.

New research has shown that a small technical change to this procedure, involving creating a small flap in the peritoneum, can more than halve the incidence of this complication. The small flap is then attached to the pelvis, thus creating a route for the lymphatic fluid to escape from the pelvis into the abdomen, where it is more easily absorbed. These findings, presented at EAU23, could reduce the incidence of lymphocele and associated symptoms, such as pain, pressure on the bladder, swollen legs, and deep vein thrombosis.

Manuel Neuberger, University Medical Centre Mannheim, and Heidelberg University, Germany, outlined: "Previous studies of the technique have been inconclusive, so we designed a larger, more robust trial to ensure our findings were statistically significant." In total, 550 patients were involved in the trial and were randomly assigned to one of two groups: with or without flap. Four surgeons performed the peritoneal flap procedure, and were only informed whether a patient was to undergo this procedure once the initial operation was complete. The patients were followed for 6 months following the operation, and factors related to the risk of lymphocele, such as diabetes, the extent to which lymph nodes were removed, whether they took anti-coagulants, and the surgeon doing the operation were taken into account.

> **"Using the peritoneal flap reduced the incidence of lymphocele from 9% to less than 4%."**

At the time of discharge, 20 patients in the peritoneal flap group had asymptomatic lymphocele, compared to 46 in the control group. During the follow-up, this had risen to 27 in the peritoneal flap group, but 74 in the control group. Thus, only 10 patients in the peritoneal flap group had developed a symptomatic lymphocele compared to 25 in the control group.

Lead researcher Philip Nuhn, University Medical Centre Mannheim, said: "Using the peritoneal flap reduced the incidence of lymphocele from 9% to less than 4%. We now use this as the new standard in Mannheim, and hope that [...] it will become common practice elsewhere as well."

Delayed Treatment of Localised Prostate Cancer Does Not Increase Mortality Risk

ACTIVE monitoring of prostate cancer has been shown to exhibit the same high survival rates after 15 years as radiotherapy or surgery, according to findings from the ProtecT trial presented at the EAU23 congress in Milan, Italy. This regular surveillance of cancer meant that males were more likely to observe progression or spread, but this was found not to reduce their likelihood of survival.

Lead investigator Freddie Hamdy, University of Oxford, UK, highlighted that the study shows treatment decisions following diagnosis of low- and intermediate risk localised prostate cancer do not need to be hasty. Hamdy said: "A diagnosis of prostate cancer should not be a cause for panic or rushed decision making… Patients and clinicians can and should take their time to weigh up the benefits and possible harms of different treatments, in the knowledge that this will not adversely affect their survival."

Funding for this study was provided by the National Institute for Health and Care Research (NIHR), involving researchers at the Universities of Oxford and Bristol, and spanning nine UK centres, as the longest investigation of its kind. ProtecT is the first full evaluation of three major treatment options for males with localised prostate cancer: active monitoring, surgery (radical prostatectomy), and radiotherapy.

The study cohort included 1,643 males aged 50–69 years who were diagnosed with localised prostate cancer from a PSA blood test. The research team followed these patients in the UK for an average of 15 years, between 1999–2009. They were randomised into active monitoring (545), radical prostatectomy (553) and radical radiotherapy (545) groups. Mortality rates, cancer progression and spread, and the impact of treatment on quality of life were all measured, with results demonstrating 97% of males diagnosed with prostate cancer survived 15 years, irrespective of the treatment they received. Close to one-quarter of patients on active monitoring had not had any invasive treatment for their cancer after 15 years, and patients from all three groups reported similar overall quality of life. This trial also found that negative impacts of radiotherapy and surgery on urinary, bowel, and sexual function persist much longer than previously thought, for up to 12 years.

Previous research had hinted at a lower survival rate for males on active monitoring over a long time period, but the results from this longitudinal study show that this is not the case, and survival rates remain similarly high across all groups. Jenny Donovan, study co-investigator from the University of Bristol, shared: "Survival no longer needs to be considered when deciding on treatment, as that's the same for all three options. Now, men diagnosed with localised prostate cancer can use their own values and priorities when making the difficult decisions about which treatment to choose."

Some of the males who subsequently died of their prostate cancer had been assessed as low risk at diagnosis, which the researchers highlighted as an issue of concern. Peter Albers, chair of the EAU's Scientific Congress Office, described the implications of this study: "The fact that the greater progression of disease seen under active monitoring didn't translate into higher mortality will be both surprising and encouraging to urologists and patients." Albers went on: "It's an important message for patients that delaying treatment is safe," and: "It's also clear we still don't know enough about the biology of this disease to determine which cancers will be the most aggressive, and more research on this is urgently needed." ●

"The fact that the greater progression of disease seen under active monitoring didn't translate into higher mortality will be both surprising."

Prediction Bladder Cancer with Urine Gene Tests

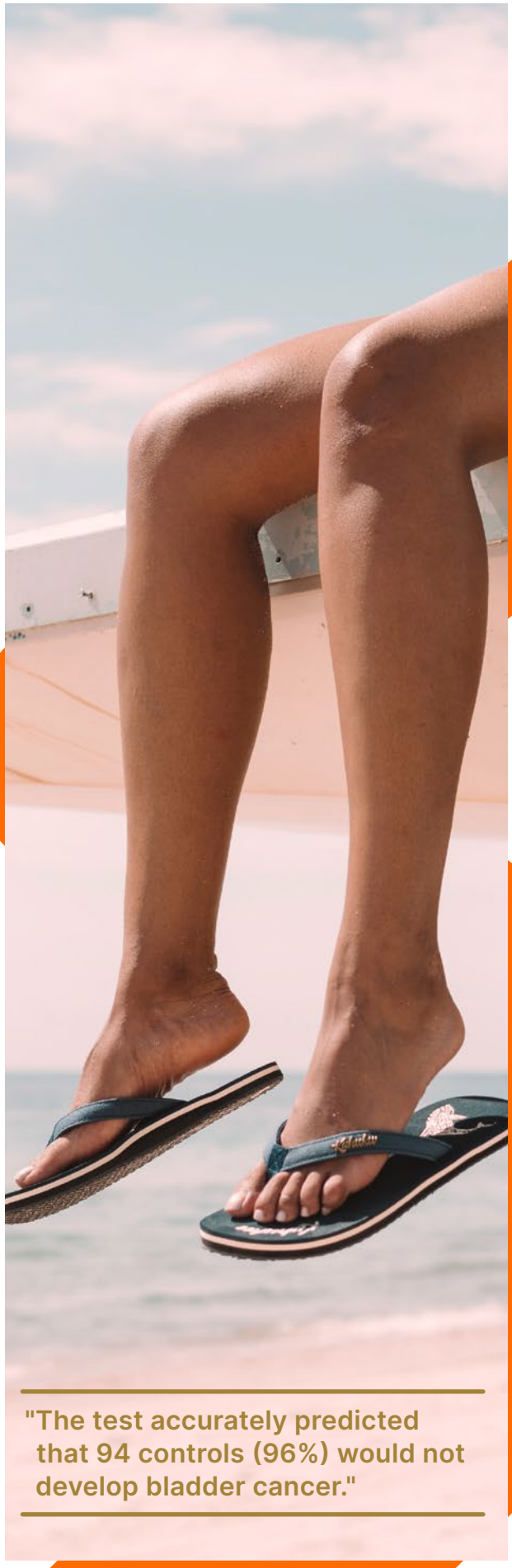
BLADDER cancer can be detected years before diagnosis by testing for genetic mutations in urine, according to new research shared at EAU23. Bladder cancer is the fifth most common cancer in the European Union (EU), with 200,000 presentations a year. While 80% of patients survive for a minimum of 5 years after diagnosis if the cancer is detected early, this drops to approximately 50% when patients are diagnosed with advanced disease, which is primarily due to late diagnosis and disease recurrence.

Inspired by previous research identifying genetic mutations associated with bladder cancer, researchers from three countries identified 10 genes that could predict the commonest type of bladder cancer up to 12 years before diagnosis.

The test was trialled at the Tehran University of Medical Sciences (TUMS), Iran, using urine samples from the Golestan Cohort Study, which had tracked the health of >50,000 participants for 10 years. While 40 people developed bladder cancer during this time, only 29 samples could be tested, along with 98 other participants as controls. The researchers were able to accurately predict future bladder cancer in 19 participants (66%), of which 12 (86%) were diagnosed within 7 years of urine collection. Furthermore, the test accurately predicted that 94 controls (96%) would not develop bladder cancer, with no cancer diagnosis being made within 6 years of urine collection.

This was further trialled at Massachusetts General Hospital, Boston, USA, and Ohio State University (OSU), Columbus, USA, with samples from 70 patients with bladder cancer from the day of diagnosis and 96 controls. Mutations were found in 50 (71%) of those with cancer whose tumours were visible during cystoscopy but were not found in 90 (94%) of controls.

Lead Researcher Florence Le Calvez-Kelm, International Agency for Research on Cancer (IARC), Lyon, France, believes that these results demonstrate the potential of genetic urine tests in predicting bladder cancer.



"The test accurately predicted that 94 controls (96%) would not develop bladder cancer."

Recommendations for Prostate Cancer Screening in Europe

Authors: Abigail Craig, Editorial Assistant

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FOR the first time, prostate-specific antigen (PSA)-based prostate cancer screening has been included in the Screening Recommendations published by the European Commission (EC). A series of presentations and discussions were held at the European Association of Urology (EAU) 2023 Congress in Milan, Italy, on how European Union (EU) member states should swiftly implement these recommendations in their own populations. Emphasis was placed on raising awareness and promoting risk stratification before biopsy to reduce overdiagnosis.

THE BURDEN OF PROSTATE CANCER ACROSS THE EUROPEAN UNION

Partha Basu, Head of the Early Detection and Prevention Branch of the International Agency for Research on Cancer (IARC), Lyon, France, presented prostate cancer specific mortality trends across the EU. While the burden of prostate cancer is high in these countries, associated mortality is largely variable. Averages across the continent show that mortality rate is more than double the EU average in some countries, such as Estonia and Slovakia, while much lower in others, such as Spain and Italy. Basu highlighted that prostate cancer incidence is often driven by the presence or absence of screening, as shown by a rise in diagnoses up until the de-escalation of screening in 2007/8. However, mortality is largely dependent on access to care and care quality. These trends can be identified in data from the USA: as screening increased so did incidence, while the late diagnosis of prostate cancer was reduced.

PROSCREEN

The subsequent discussion centred around updates from numerous ongoing trials. One of these detailed was ProScreen, a large population-based screening trial that aims to reduce overdiagnosis while retaining or increasing the impact of prostate cancer screening on mortality. Anssi Auvinen, Tampere University, Finland, outlined that ProScreen is the only trial with prostate cancer mortality as the endpoint, describing it as "the gold-standard for screening; it represents the real benefit of screening, and it is not prone to bias like other intermediate outcomes."

> **"Averages across the continent show that mortality rate is more than double the EU average."**

The study included males aged 50–63 who were randomised to either a screening arm or a control arm in a ratio of 1:3. Those randomised to the screening arm underwent three sequential tests; a PSA test, 4Kscore test, and an MRI. Only those with concerning results in all three tests were referred for a targeted biopsy. The first screening round of 60,784 males is almost complete, despite delays caused by COVID-19, and so far, around 330 cases of prostate cancer have been identified in the control arm. Participants with a baseline PSA of >3.0 ng/mL and 1.5–3.0 ng/mL have since been screened after a follow-up delay of 2 and 4 years, respectively. Results for this follow-up are currently under analysis and are set to be presented at the EAU24, where the

emphasis will be on the accurate detection of prostate cancer through screening without overdiagnosis.

PROBASE

This session also included an update on PROBASE, a randomised trial aiming to determine the efficacy of risk adapted PSA screening in males aged 45 or 50. According to the baseline PSA taken at each of these ages, participants were stratified into three groups; low- (PSA: <1.50 ng/mL), intermediate- (PSA: <1.50–2.99 ng/mL), and high-risk (PSA: >3.00 ng/mL).

The low and intermediate risk groups underwent a second PSA test after 5 and 2 years, respectively. Meanwhile, the high-risk group underwent a multiparametric MRI and biopsy. The initial pool of 23,301 males identified 186 high risk cases (0.8%). Following biopsy, prostate cancer was diagnosed in 48 individuals, with most being low grade cancers (44 out of 48; 91.7%). In the deferred screening arm for low- and intermediate-risk participants, 57 digital rectal examinations produced abnormal results. In 37 of these patients, a biopsy was performed, identifying two cases of low grade (ISUP1) prostate cancer.

In summary, Kathleen Herkommer, Technical University of Munich, Germany, recommended that the "indication for further diagnostic tests should be based on a confirmed PSA value," and that the rate of cancer detection using digital rectal examination is extremely low.

15 YEARS OF PROTECT

Freddie Hamdy, University of Oxford, UK, and Jenny Donovan, University of Bristol, UK, also provided updates on the ProtecT trial. Between 1999–2009, 82,429 PSA tests were conducted across nine UK centres, with 2,965 cancers being diagnosed and 1,643 patients assigned to active monitoring (545), radical prostatectomy (553), or radical radiotherapy (545).

After 15 years of follow-up, 72% of patients allocated to active monitoring had switched to radical treatment. Surprisingly, the prostate cancer specific survival probability of each of the treatment groups remained largely the same for up to 17 years. Regarding metastases, there was a 50% reduction in incidences for the active monitoring group, but this is yet to translate into differences in mortality. Hamdy addressed misconceptions about the study, emphasising that ProtecT is not just a low-risk cohort of

males with prostate cancer, as 34% of patients were classified as intermediate-risk. Hamdy also stressed that ProtecT is not disputing the need for aggressive treatment in high-risk prostate cancer. Although the active monitoring utilised by ProtecT is less intense than contemporary active surveillance, cancer survival showed no difference compared to radical treatments.

> **"Donovan hopes these results can help newly diagnosed patients with localised prostate cancer."**

Donovan focused on patient-reported outcomes 12 years after treatment. The ProtecT study questionnaire was answered annually, and centred around urinary, bowel and sexual function, and the subsequent impact on quality of life. After 12 years, 24% of patients in the prostatectomy, 11% of patients in the active monitoring, and 8% of patients in the radiotherapy treatment groups experienced urinary leakage. Levels of sexual potency slowly declined across all groups, reaching a minimum at 12 years post-treatment. Donavan described the path to the minimum value as different for each treatment group, but most importantly the active monitoring group reported increased sexual function compared to the radical treatment groups at all timepoints. There was no difference reported for bowel function across the three groups, but when specifically considering faecal leakage, rates were highest in the radiotherapy group (12%). Overall, side effects of radical treatments can continue to affect the lives of males 12 years after treatment. Donovan hopes these results can help newly diagnosed patients with localised prostate cancer assess the trade-offs between the benefits and harms of treatment options.

CLOSING REMARKS

Presentations later centred around the use of genetic biopsies to promote active surveillance in Grade 2 prostate cancers and the appropriateness of MRI in this setting.

Overall, these presentations provided thought-provoking discussions around the appropriate management of prostate cancer. Following these new cancer screening recommendations, a stepwise approach to evaluating the feasibility and effectiveness of organised prostate cancer screening programmes should be undertaken.

Open Versus Robotic Surgical Approach for Ileal Conduit Formation

Authors: Jivitesh Newoor, Editorial Assistant

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DURING the European Association of Urology (EAU) Congress 2023, experts participated in a series of debates regarding the use of robotic versus open surgical techniques, including a key focus on ileal conduit formation.

OPEN SURGERY APPROACH FOR AN ILEAL CONDUIT FORMATION

After undergoing a radical cystectomy (RC), an ileal conduit (IC) is the most common urinary diversion technique performed by urologists, where the ileum is used as an alternative pathway for urine to exit the body. The first debate focused on the procedure for forming an IC, with Óscar Rodríguez Faba, Fundació Puigvert, Spain, advocating for open ileal conduits. Acknowledging that robotics is becoming an important component in the field, Faba highlighted that currently in England more than 50% of IC procedures are open. Faba added that the current literature establishes that open ICs are the gold standard, and all novel techniques must be compared with open ICs.

ADVANTAGES OF OPEN SURGERY

Faba detailed the components involved when forming an IC , and listed the advantages of open surgery, where surgeons can measure length and trans-illuminate to ensure a healthy ileal loop. During hand-sewn end-to-end bowel anastomosis, surgeons can ensure the suture has sufficient tension, and better understand the quality of the anastomosis. The stoma can be performed in a very practical manner during open surgery, with the surgeon using their finger as a final intervention to make sure there is a good passage for urine. Faba stressed that these aspects cannot be easily replicated with the robotic approach. The use of indocyanine green is required, and this has proven to be significantly more expensive.

In terms of quality of life, there were no differences in outcomes between open surgery and robotic IC. However, Faba emphasised the difference in cost is significantly more for a mechanical anastomosis, where a staple costs around 1,250 EUR compared to a hand-sewn anastomosis, where the cost is negligible. In some cases, robotic ICs can cost over 2,000 EUR more.

Faba discussed complications reported by randomised controlled trials (RCTs). Findings from the RAZOR study revealed no differences in terms of intestinal complications, or in any of the parameters from a digestive aspect. Furthermore, the CORAL trial also reported no differences in complications.

Faba concluded by suggesting that to improve robotic surgery, all the surgical steps that have been described in open surgery should be reproduced in robotic surgery. Faba stated: "The gold standard is still open IC, and we shall see in the future whether the multicentre RCTs can change this statement."

> **"The gold standard is still open IC, and we shall see in the future whether the multicentre RCTs can change this statement."**

ROBOTIC APPROACH FOR AN ILEAL CONDUIT FORMATION

Véronique Phé, Sorbonne University, Paris, France, advocated for use of robotic ileal conduits. Phé stated that robotic-assisted radical cystectomy (RARC) is being performed with increasing frequency, and given the prevalence of coexisting comorbidities, patients undergoing RC may benefit from robotics. Phé highlighted that no proven benefits in both perioperative and oncological outcomes have been described in the RCTs that compared RARC and open RC.

ADVANTAGES OF ROBOTIC SURGERY

Phé emphasised that the question should not only focus on robotic IC versus open IC. Instead, it should incorporate intracorporeal RARC versus extracorporeal RARC. Phé underlined that most surgeons currently use the extracorporeal urinary diversion (ECUD) technique because it is simpler and faster to perform. However, the use of intracorporeal urinary diversion (ICUD) has significantly increased in the last decade. Although robotic surgery is technically more challenging, the advantages include a reduced number of incisions, and it can be performed faster because there is no need to undock or create a new incision to close.

Phé discussed whether ICUD can improve outcomes, highlighting findings that demonstrated that patients undergoing complete RARC spent more time out of the hospital than those receiving open surgery. Phé highlighted that extended hospital stays can be significantly more costly. The second endpoint, which measured the qualitative recovery from different parameters, favoured robotic surgery at 5 weeks. Additionally, there were fewer wound complications with the complete robotic approach, and there were no differences in cancer recurrence and overall mortality.

Studies comparing ICUD and ECUD found that all parameters, including operating time, blood loss, blood transfusion, and high-grade complications, favoured the intracorporeal approach. Although there were more high-grade complications with ICUD than ECUD, Phé affirmed that

these complications decreased with time and experience. When performed by an experienced surgeon, ICUD may offer reduced estimated blood loss, lower pain, smaller incisions, and a quicker return to bowel function. Phé acknowledged that the potential disadvantages included a longer learning curve, technical challenges, and longer operation times.

Phé concluded that the total ICUD approach holds the potential to improve perioperative parameters without impairing oncological performance of the procedure, and emphasised that much of the benefit from robotic operations occurs immediately after surgery. Notably, Phé highlighted that the key variable is the skill and experience of the surgical team, regardless of whether robot assistance is used.

An important question raised in discussion was whether surgeons should be trained in open surgery before robotic, as this is often essential. However, Faba declared their uncertainty. There are generations of surgeons who are untrained in open surgery, and underscored how much open surgeons have learned from robotic surgery. To improve immediate outcomes, aspects from open surgery can be applied to robotic surgery.

CLOSING REMARKS

A recurring theme throughout this session, which included two further debates on open versus robotic approaches and a presentation by Christopher Chapple, EAU Secretary General, was that the most significant difference between robotic and open surgery was dependent on the surgeons' training and experience, rather than the technique itself. ●

"The most significant difference between robotic and open surgery was dependent on the surgeons' training and experience, rather than the technique itself."

Androgen Deprivation Therapy in Current Clinical Practice: Challenges and Future Perspective

This article details the use of androgen deprivation therapy in current clinical practice as discussed in an Accord Healthcare-sponsored symposium, delivered as part of the European Association of Urology (EAU) 38th Annual Congress held in Milan, Italy, between 10th–13th March 2023

Chairperson:	Heather Payne[1]
Speakers:	Kurt Miller,[2] Alberto Bossi,[3] Patrick Davey[4]

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2. Charité University Hospital, Berlin, Germany
3. Amethyst Group, Institut Gustav Roussy (IGR), Paris, France
4. Northampton General Hospital, UK

Disclosure:	Payne has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas Pharma, Janssen, Sanofi Aventis, Ferring Pharmaceuticals, Bayer, Novartis, and Accord. Miller has acted as an adviser for and has received honoraria from Accord, Astellas Pharma, Bayer, Ferring Pharmaceuticals, Janssen, MSD, Novartis, Pfizer, and Roche. Bossi has received research support from Ipsen and Janssen; is an employee of RT Amethyst Group, France; is a consultant for Astellas Pharma, Bi-Protect, Ipsen, and Myovant; has served on a speaker's bureau for Astellas Pharma, Bristol Myers Squibb (BMS), Elekta, and Ferring Pharmaceuticals; has received honoraria from Astellas Pharma, Elekta, Ipsen, Janssen, Ferring Pharmaceuticals, and Sanofi; and has participated in scientific advisory boards for Astellas Pharma, Elekta, Ipsen, Ferring Pharmaceuticals, and Myovant. Davey has collaborated with Boehringer Ingelheim, Ferring Pharmaceuticals, AstraZeneca, Daiichi Sankyo UK, Eli Lilly and Company, Consultant Connect, and iRhythm.
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Disclaimer:	The opinions expressed in this article belong solely to the named speakers. ORGOVYX (relugolix) is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer. **Prescribing information for ORGOVYX▼ (relugolix) can be found here and the 'AE reporting statement' can be found at the end of the article.**
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Meeting Summary

Androgen deprivation therapy (ADT) has been used for many years for treating advanced prostate cancer (PCa) and remains the backbone of treatment. Luteinising hormone-releasing hormone (LHRH) receptor agonists are the most widely used ADT drugs. However, newer options, including gonadotropin releasing hormone (GnRH) receptor antagonists such as degarelix and relugolix, may be clinically more beneficial for some patients. GnRH antagonists reduce serum testosterone levels more rapidly than LHRH agonists, without an initial testosterone surge or subsequent microsurges.

This article summarises a symposium delivered on 11th March 2023 at the 38th European Association of Urology (EAU) Annual Congress in Milan, Italy, where speakers from three different disciplines described challenges and future perspectives for ADT in current clinical practice. Kurt Miller, Urologist, Charité University Hospital, Berlin, Germany, described the evolution of ADT in the treatment of PCa, from early reports of the benefits of surgical castration to the recent development of oral treatment for chemical castration. Miller explained the acceleration in progress in ADT research over recent years, with the development of novel drugs, drug sequences, and combinations, which have transformed outcomes in PCa. Alberto Bossi, Radiation Oncologist, Amethyst Group, Institut Gustav Roussy (IGR), Paris, France, next described current challenges with ADT management, including outstanding questions about the personalisation of ADT. Finally, Patrick Davey, Consultant Cardiologist, Northampton General Hospital, UK, spoke about ways to maintain a healthy heart on hormone treatment, and noted that cardiovascular safety is a major challenge in the use of ADT.

The meeting was chaired by Heather Payne, Consultant Clinical Oncologist, University College Hospital, London, UK, who introduced the speakers and co-ordinated a question-and-answer session at the end of the symposium.

Introduction

ADT, via medical or surgical castration, has been the mainstay of treatment for PCa for decades.[1,2] ADT is currently most often achieved through the use of LHRH agonists such as leuprolide, goserelin, and triptorelin, which are administered subcutaneously or intramuscularly.[1] These agents stimulate the LHRH receptor on Leydig cells in the testes, causing a temporary surge in testosterone levels before negative feedback, which results in receptor downregulation and leads to the suppression of testosterone release, reaching levels below castration (<50 ng/dL) within 4–6 weeks.[1]

More recently, GnRH antagonists such as degarelix and relugolix have been developed. These agents suppress the secretion of testosterone from the testes by binding competitively to the GnRH receptor in the pituitary gland, inhibiting release of the luteinising hormone and follicle-stimulating hormone, and thereby reducing downstream gonadotropin signalling.[1] As GnRH antagonists do not cause an initial surge of serum testosterone, and can achieve castration levels within 2–3 days, they are proving to be a good therapeutic option for some patients with PCa.[1] Relugolix also has the advantage that it may be administered orally, providing greater flexibility for patients.[1]

In the Accord Healthcare-sponsored symposium, 'ADT in current clinical practice: Challenges and future perspective', delivered on 11th March 2023 at the 38th EAU Annual Congress in Milan, Italy,

speakers from three different specialties guided delegates through the development of ADT in PCa, from the earliest reports of the benefits of surgical castration in the 1960s to the generation of multiple new classes of ADT in recent years. Current challenges associated with ADT were also discussed, including questions around the combination of radiotherapy (RT) and ADT, and whether co-administration with a high dose of RT directly to the prostate may allow the duration of ADT to be reduced. Finally, the importance of cardiovascular (CV) safety in the use of ADT was considered, including an overview of the different levels of risk for different drugs, as well as insights into how to protect patients against the risk of CV events.

The Evolution of Androgen Deprivation Therapy in the Treatment Algorithm of Prostate Cancer

Kurt Miller

Miller opened the symposium by providing a short walk through the history of ADT, with its many twists and turns. They noted that many opportunities for learning had been encountered along the way, as is the case in most branches of medicine, but that progress had accelerated considerably in recent years.

The history of ADT for the treatment of PCa dates back to 1941, when Charles B. Huggins published their first paper on the effects of surgical castration (orchiectomy) on advanced carcinoma of the prostate gland.[3] Huggins discovered that androgens, specifically testosterone, play a significant role in the growth and progression of PCa, and that suppressing serum testosterone levels increased life expectancy and reduced hours spent in pain.[4] Huggins was eventually awarded the Nobel Prize for Medicine in 1966 for this pioneering work in treatment of advanced and metastatic PCa.[1]

Despite the successes of ADT, Miller noted that this treatment approach is not without side effects, including sexual dysfunction, hot flushes, osteoporosis/clinical fractures, metabolic syndrome, CV events, fatigue, depression, and sleeping disturbance.[5] Miller noted that although these are not devastating consequences, both patients and physicians should be aware of the risk of these effects and how to manage them.

Following the initial work by Huggins, many studies evaluating different approaches to testosterone suppression for treating PCa were subsequently undertaken.[1] Among these, the Veterans Administration Cooperative Urological Research Group (VACURG) studies conducted between 1960–1971 investigated the use of testosterone suppression using oestrogen in the form of diethylstilbesterol (DES).[6] These studies showed that while a dose of 5 mg DES actually led to poorer survival outcomes compared with placebo, a 1 mg dose of DES increased survival rates compared with both higher DES doses and placebo.[6] Miller commented that although they were still using oestrogens for castration-resistant PCa approximately 20 years ago, when there were no other alternative treatments, this treatment approach was largely discarded in the 1970s.

In the 1970s, another Nobel Prize was earned in this field when the father of LHRH agonists, Andrew Schally, discovered that serum testosterone levels were suppressed by constant exposure to LHRH, which downregulated the LHRH receptors, leading to desensitisation of pituitary cells.[1,7] This discovery led to the development of LHRH agonists, which became a mainstream of treatment for PCa in the 1990s.[1] Miller noted how the development of LHRH agonists led to the demise of orchiectomy for PCa, which had been the standard treatment in the 1970s and 1980s.

Miller next described how anti-androgens were introduced as new potential approach in the management of PCa. Instead of lowering testosterone levels, anti-androgen agents compete with androgens at the receptor level.[8] Miller observed, however, that this approach never became mainstream as monotherapy for PCa, except in specific circumstances. Complete androgen blockade, using a combination of anti-androgens and LHRH agonists to block the androgens originating from both the testes and the adrenal gland, was subsequently proposed as a new approach to treatment for prostate cancer.[9] The first reports indicated that complete androgen blockade may be able to cure at least 90% of cases of PCa, although subsequent studies revealed that the addition of an anti-

androgen therapy improved absolute survival by approximately 2–3% only.[10] Miller noted that the pursuit of effective complete androgen blockade represents another detour in the development of ADT for PCa.

The use of intermittent androgen blockade began to emerge as the next potential route in the management of PCa, on the basis that it may delay the onset of hormone resistance.[11] However, no survival benefit was demonstrated for intermittent androgen blockade compared with continuous therapy, although some studies showed the results to be non-inferior and associated with some improvement in quality of life.[11]

The development of LHRH agonists and GnRH antagonists marked the beginning of a new era in the management of PCa.[12] While LHRH agonists cause an initial testosterone surge that may result in a clinical flare of symptoms,[13] GnRH antagonists have been shown to offer rapid reduction of serum testosterone without the initial testosterone surge and symptoms flare.[1] The Phase III HERO study revealed rapid testosterone suppression to castration levels with the first oral GnRH antagonist, relugolix, which were then maintained throughout the treatment period.[13] In contrast, the LHRH agonist leuprolide caused an initial surge in testosterone levels, before decreasing to and remaining at castration levels.[13] The overall incidence of adverse events was consistent across treatment groups of the two agents,[13] although there was a 54% reduction in risk of major adverse cardiovascular events (MACE) with relugolix versus leuprolide, as discussed later.[14]

Miller concluded their presentation by noting that little notable improvement in ADT efficacy was achieved for approximately 70 years following the early discoveries in 1941. However, progress rapidly accelerated after 2012, with multiple trials showing Level 1 evidence for improved overall survival (OS) in metastatic hormone sensitive PCa (Table 1). Miller noted that with new combination therapies, new drugs, and advances in cancer research, the future looks promising for patients with PCa undergoing ADT.

Table 1: Level 1 evidence for improved overall survival in metastatic hormone-sensitive prostate cancer.

Clinical Trial	Intervention	Control	Comments*
STAMPEDE-H[15]	Prostate radiation+ADT (±docetaxel)	ADT (±docetaxel)	Benefit in low-volume subgroup
GETUG AFU-15[16] **CHAARTED**[17] **STAMPEDE-C**[18]	Docetaxel+ADT	ADT	Benefit in high-volume subgroup
LATITUDE[19] **STAMPEDE-G**[20]	Abiraterone+ADT	ADT	Similar benefits by risk group
ARCHES[21] **ENZAMET**[22]	Enzalutamide+ADT	ADT	Similar benefits by risk group
TITAN[23]	Apalutamide+ADT	ADT	Similar benefits by risk group
ARASENS[24]	Darolutamide+ ADT+docetaxel	ADT+docetaxel	Similar benefits for recurrent and *de novo* metastatic disease
PEACE-1[25]	Abiraterone+ADT+docetaxel (±prostate radiation)	ADT+docetaxel (±prostate radiation)	Subgroup analysis

*Comments reflect the views of the speaker.

ADT: androgen deprivation therapy.

Current Challenges with Androgen Deprivation Therapy Management

Alberto Bossi

Bossi gave the second presentation in the symposium, describing current challenges associated with the use of ADT, particularly in combination with RT. They noted that a high dose of RT is needed in the prostate to control the disease, irrespective of the method used for delivery, and the combination of RT and ADT gives better survival outcomes than either RT alone or ADT alone.[26-31] However, Bossi noted that many of the studies are now several years old, and should ideally be repeated in the light of more recent developments in treating PCa. The findings of these studies are reflected in the current EAU Guidelines, which recommend long-term (2–3 years) ADT in high-risk patients with locally advanced disease and short-term (6 months) ADT in patients with unfavourable intermediate disease, while ADT is not recommended to treat patients with favourable intermediate disease.[8]

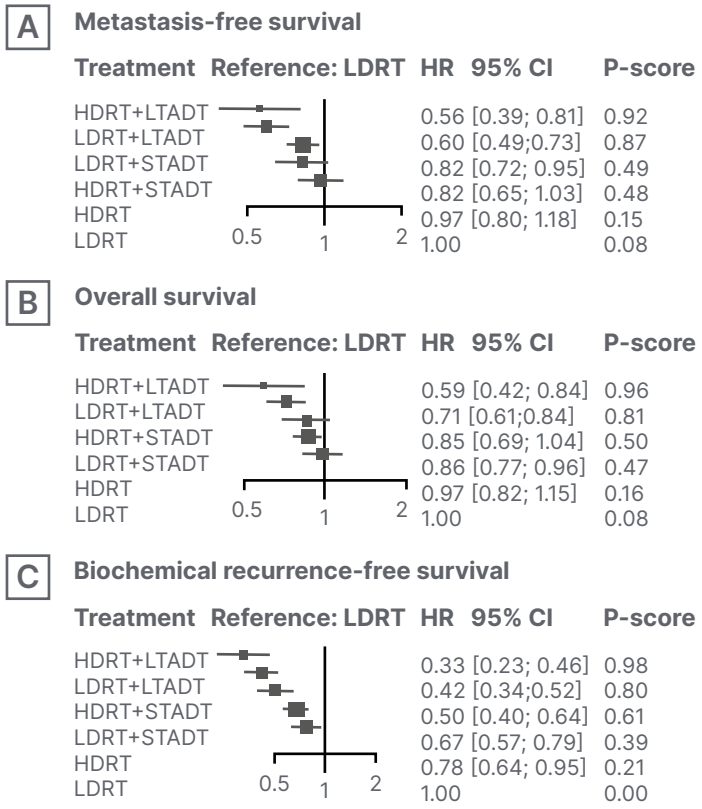
Despite all the evidence accumulated to date demonstrating the benefit of ADT and RT combination therapy in improving survival in PCa, Bossi noted that several unanswered questions remain. Among the issues that require further investigation is the current uncertainty around how long ADT should be administered with RT, and when treatment should be initiated. A meta-analysis of 12 randomised controlled trials (RCT), including more than 10,000 patients with intermediate- or high-risk disease, with median follow-up 11 years, confirmed that long-term ADT is better than short-term ADT in terms of metastasis-free survival or OS,[32] as expected. However, they found no impact on metastasis-free survival or OS when adding neoadjuvant ADT to adjuvant ADT, meaning that there is no advantage in initiating ADT prior to RT. Bossi noted that this is contrary to common clinical practice, when patients may be given ADT while they are on the waiting list for RT therapy, or because physicians believe instinctively that this may offer some survival advantage.

Bossi commented that a second unanswered question in this area concerns whether delivering a high dose of RT directly to the prostate may allow the dose of ADT to be reduced, potentially improving the quality of life of the patient. A second meta-analysis, this time including 13 RCTs with more than 11,000 patients with intermediate- or high-risk disease and a median follow-up of 9 years, investigated the effect of low-dose RT (<74 Gy) versus high-dose RT (≥74 Gy), and short-term ADT (3–6 months) versus long-term ADT (18–36 months) on OS.[33] This analysis revealed that long-term ADT rather than high-dose RT was the most important factor in improving both metastasis-free survival and OS, although there appeared to be some advantage to giving high-dose RT in terms of biochemical recurrence-free survival (Figure 1).

Bossi observed that one further challenge regarding the use of RT plus ADT in PCa was the relative toxicity of ADT. Although use of ADT is not recommended in low-risk PCa due to the lack of benefit and potential for harmful side effects, the National Cancer Database (NCDB) shows that a declining proportion of patients are still receiving ADT for low-risk PCa.[34] Bossi noted that the best way to reduce ADT toxicity was to avoid ADT when it is unnecessary, for example as concurrent treatment for low-risk disease (including in preparation for local delivery of RT using brachytherapy). In addition, ADT should not be used as the sole primary therapy (without RT) for localised/high-risk PCa. Bossi described a potential strategy for reducing the overall requirement for ADT using brachytherapy (implantation of a sealed radiation source at the site where radiation is to be delivered) to boost the effect of externally-delivered RT, allowing a reduced duration of ADT.[35] They also suggested that the use of ADT may be tailored through genetic profiling to create clinical-genomic risk groups that could be incorporated into treatment guidelines for localised PCa.[36]

Bossi concluded that ADT plays an essential role in the treatment of patients with high-risk PCa, and that combining it with RT has shown to have significant benefits in terms of OS. However, they noted that optimising the use of ADT to reduce toxicity and avoid unnecessary use remains an ongoing challenge for clinicians.

Figure 1: Forest plot derived from frequentist network meta-analysis of impact of treatment strategy on survival outcomes.[33]



Adapted from Kishan et al.[33]

CI: confidence interval; HDRT: high dose radiotherapy; HR: hazard ratio; LDRT: low dose radiotherapy; LTADT: long-term androgen deprivation therapy; STADT: short-term androgen deprivation therapy.

A Healthy Heart on Hormone Treatment (Androgen Deprivation Therapy)

Patrick Davey

The final talk given by Davey, a consultant cardiologist, focused on the increased risk of CV events with ADT and the impact of this risk on survival. They also considered differences in the risk of CV events between LHRH agonists compared with GnRH antagonists, and looked at ways to prevent CV adverse events, with guidance and practical tips for urologists.

Davey presented results of a Swedish nationwide population-based study showing that there was considerable CV disease (CVD) across the whole spectrum of disease among males with localised PCa, irrespective of PCa risk category or presence of comorbidities.[37] Indeed, for low-risk PCa, PCa itself was actually only the third most common cause of death (18%), after CVD (31%) and other cancers (30%).

Among patients with PCa and pre-existing CVD, those with coronary artery disease have a small but definite increase in the risk of death (adjusted hazard ratio [HR] versus no coronary artery disease or stroke: 1.05; 95% confidence interval [CI]: 1.00–1.10), while patients who have had a stroke have a much greater increase in the risk of death (adjusted HR: 1.20; 95% CI: 1.12–1.30), possibly because of the greater functional impact associated with stroke compared with coronary artery disease.[38] Even in patients with metastatic PCa, CVD still plays a significant role in determining mortality rates, as shown by data from the Surveillance, Epidemiology, and End Results (SEER) programme.[39] Among 26,168 males with metastatic PCa, 16,732 died during

the observation period (2000–2016), including 13,011 deaths from PCa and 1,147 deaths from CVD (standardised mortality ratio: 1.34). However, the SEER database does not include data on ADT exposure.[39]

In a real-world study of patients with metastatic PCa receiving conventional ADT, in which 32% of patients had pre-existing CVD, mortality rates were 50% higher in those with established CVD (14.8% versus 9.8% overall), while CV death also increased with age and increasing Charlson Comorbidity Index (CCI).[40] This study showed that between the lowest and highest comorbidity cohorts, there was no change in PCa-specific mortality, a four-fold increase in CV mortality, and a two-fold increase in other-cause mortality, demonstrating the importance of preventing CV events in these patients.

Although early PCa drug treatments, including oestrogen, showed promise in improving PCa, any survival benefit was undermined by an increased CV risk.[6] Concerns over CV risk in new generations of therapy became increasingly prominent from around 2005 onwards. Interestingly, observational studies tend to show an increased risk of MACE with ADT, mostly LHRH agonists, although the same risk is not always apparent in RCTs.[41] For example, a population-based study from Sweden showed an increased relative risk of non-fatal and fatal CVD among all males with PCa, especially those treated with ADT.[42] The reasons for the apparent difference between population-based studies and RCTs in this regard are not entirely clear, and may be due to inclusion criteria for RCTs (patients with high CV risk are more likely to be excluded) or reporting bias.

There is evidence to suggest that GnRH antagonists may be associated with a lower CV risk than LHRH agonists. For example, a 2014 pooled analysis of six Phase III trials of degarelix versus an LHRH agonist showed lower CV risk with the GnRH antagonist versus LHRH agonists in males with pre-existing CVD (HR: 0.44; 95% CI: 0.26–0.74; p=0.002).[43] A similar finding was reported in a small prospective Israeli study, which showed that patients treated with an LHRH agonist experienced significantly more major CV and cerebrovascular events than those treated with a GnRH antagonist.[44] However, in the PRONOUNCE study, the first international RCT to prospectively compare the CV safety of a GnRH antagonist and a LHRH agonist in patients with PCa, no difference in MACE was observed at 1 year between patients assigned to degarelix versus leuprolide, although the study was stopped early due to poor recruitment.[45] Davey made the point that all patients in the study had seen a cardiologist, which may have improved CV safety in both groups and obscured any difference between groups. More recently, the HERO trial, described previously, showed an approximate halving of risk of MACE in the relugolix group compared with the leuprolide group.[14]

Overall, Davey concluded that CVD is common in PCa and worsens prognosis, and that LHRH agonists probably increase MACE, with the greatest increase in risk seen among those with pre-existing CVD. They also noted that GnRH antagonists are probably associated with lower CV risk than LHRH agonists, and concluded their presentation by considering the actions that can be taken to prevent CV events. Davey noted that management of CV risk should be based on lifestyle changes, exercise, strategies to reduce blood pressure and cholesterol, aggressive intervention for known CVD, and referral to a cardiologist for CV symptoms. They also presented the ABCDE of CV risk management: awareness and aspirin; blood pressure; cholesterol, cigarettes, and cardiologist; diet and diabetes; and exercise. Davey finally presented the European Society of Cardiology (ESC) guidelines, which offer specific recommendations for baseline risk assessment and monitoring during ADT for PCa (Table 2).[46]

Conclusion

The presentations given in this symposium summarised the progress that has been made in ADT for PCa since the 1940s. It was noted that after the initial Nobel Prize-winning discovery of the benefits of surgical castration in prolonging life in patients with PCa, the rate of progress in terms of new treatments and innovations remained slow until 2012, when there was a sudden rush of new treatments developed and approved, which have offered significant benefits to patients since. However, despite the recent advances, certain questions and issues remain,

Table 2: Recommendations for baseline risk assessment and monitoring during androgen deprivation therapy for prostate cancer.[46]

Recommendation	Class	Evidence level
Baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended in patients treated with ADT without pre-existing CVD	I	B
Baseline and serial ECGs are recommended in patients at risk of QTc prolongation during ADT therapy	I	B
A GnRH antagonist should be considered in patients with pre-existing symptomatic CAD who require ADT	IIa	B
Annual CV risk assessment is recommended during ADT	I	B

Adapted from ESC 2022.[46]

ADT: androgen deprivation therapy; CAD: coronary artery disease; CV: cardiovascular; CVD: cardiovascular disease; GnRH: gonadotropin releasing hormone; QTc: corrected QT interval.

which will need to be resolved in the future. For example, the relative safety and effectiveness of LHRH agonists and GnRH antagonists will need to be explored further, as well as the role of ADT in combination with RT. Improvements in genetic profiling may help determine which patients are likely to receive the maximum benefit from ADT, meaning that those unlikely to derive a clear benefit may be spared from the potentially harmful side effects. Finally, more work remains to be done to assess CV safety in ADT, in creating strategies to mitigate the risk, and developing new treatment protocols with CV risk at the centre.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.

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Abstract Reviews

Sharing insights from abstracts presented at the European Association of Urology annual meeting, the following overviews are written by the researchers themselves, and detail some of the latest fascinating studies which are being carried out in this specialty.

^{68}Ga-Prostate-Specific Membrane Antigen PET Radiomics For the Prediction of Post-Surgical International Society of Urological Pathology Grade in Patients with Primary Prostate Cancer

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Keywords: International Society of Urological Pathology (ISUP) grade, PET, prostate cancer, prostate-specific membrane antigen (PSMA), radiomics.

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INTRODUCTION

Radiomics has been proven effective for the characterisation of primary prostate cancer (PCa).[1,2] However, the limited interpretability of the proposed models represents one of the major limitations in this field.[3,4] This study investigated ^{68}Ga-prostate-specific membrane antigen (PSMA) PET radiomics for the prediction of post-surgical International Society of Urological Pathology (ISUP) grade in patients with primary PCa, ensuring model interpretability.

MATERIALS AND METHODS

Forty-seven patients with PCa were examined with ^{68}Ga-PSMA PET at the authors' institution. Those patients were enrolled in this study prior to radical prostatectomy. Images were acquired using either PET/MRI or PET/CT. ISUP grade was available at both biopsy and radical prostatectomy for all patients. A radiologist manually segmented the whole prostate on PET images using the co-registered CT or MRI for anatomical localisation on 3D Slicer software (Brigham and Women's Hospital, Boston, Massachusetts, USA).[5] The whole prostate was used as volume of interest (VOI) to avoid the limitations of radiomics for small volumes.[6] VOIs were normalised, resampled, and discretised. A total of 103 image biomarker standardisation

Table 1: Performance of the generated models.

	Model	Balanced accuracy (%)	Sensitivity (%)	Specificity (%)	Positive predicted value (%)	Negative predicted value (%)
Logistic regression	Radiomics baseline	70.6	67.2	74.0	85.8	55.8
	PET zeros	77.4	72.2	82.7	90.9	61.9
	1 RF	79.2	77.7	80.6	90.5	66.7
	2 RFs	87.5	88.3	86.7	93.8	81.1
	3 RFs	86.5	89.7	83.3	92.9	82.3
	4 RFs	86.3	85.9	86.7	94.4	77.6
Support vector machine	Radiomics baseline	69.6	60.5	78.7	87.3	51.8
	PET zeros	76.3	69.3	83.3	91.3	60.3
	1 RF	77.9	73.7	82.0	91.0	64.2
	2 RFs	87.3	87.9	86.7	94.0	80.8
	3 RFs	87.6	88.6	86.7	94.0	82.5
	4 RFs	87.1	88.3	86.0	93.8	80.9
K nearest neighbour	Radiomics baseline	64.8	61.6	67.9	82.4	48.0
	PET zeros	72.7	68.7	76.7	87.6	56.6
	1 RF	74.1	65.3	82.7	90.6	54.8
	2 RFs	81.3	82.6	80.0	91.1	69.8
	3 RFs	81.2	82.5	80.0	90.4	70.3
	4 RFs	81.2	82.3	80.0	91.5	73.4

RF: radiomic features.

initiative-compliant, radiomic features (RF) were extracted using PyRadiomics (Python Software Foundation, Beaverton, Oregon, USA).[7] RFs were harmonised with the ComBat method[8] to control for the scanner effect, and selected using the minimum redundancy maximum relevance algorithm. Combinations of the four most relevant RFs were used to train 12 radiomics machine learning models for the prediction of post-surgical ISUP ≥4 versus ISUP <4 that were validated by five-fold repeated stratified cross-validation. To ensure that results were not driven by spurious associations, two ad hoc control models were generated. The first one

had SUVmax and VOI volume as input (radiomics baseline), while the other was made by setting to zero all voxel values prior features extraction (PET zeros). Balanced accuracy, sensitivity, specificity, and positive and negative predictive values were collected. The performance of the best developed model was compared with that of ISUP grade biopsy.

RESULTS

ISUP grade at biopsy was upgraded in 9 out of 47 patients after prostatectomy, resulting in a balanced accuracy of 85.9%; sensitivity of 71.9%; specificity of 100.0%; positive predicted value of 100.0%; and negative predictive value of 62.5%. The best performing radiomic model yielded a balanced accuracy of 87.6%; sensitivity of 88.6%; specificity of 86.7%; positive predicted value of 94.0%; and negative predicted value of 82.5%. All radiomic models trained with at least two RFs (grey level size zone matrix; zone entropy and shape; least axis length) outperformed the control models. Conversely, no significant differences were found for radiomic models trained with two or more RFs (Mann–Whitney U test; $p>0.05$). See Table 1 for a detailed report of all the generated models' performance.

CONCLUSION

These findings support the role of ^{68}Ga-PSMA PET radiomics for the accurate and non-invasive prediction of post-surgical ISUP grade. Future multicentre studies will be needed to establish with certainty the accuracy and reproducibility of the radiomic signature proposed here.

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SuPARnostic: An Advanced Predictive Tool for Detecting Recurrence in Renal Cell Carcinoma

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BACKGROUND AND AIMS

Renal cell carcinoma (RCC) is the most common malignant kidney tumour, with clear cell RCC (ccRCC) accounting for 70–80% of all cases.[1] Approximately 15–20% of patients have primary metastatic RCC at diagnosis, and 15–20% of those who receive curative treatment for localised tumours will experience recurrence within 5 years of follow-up.[2] Despite standard radiological imaging follow-up protocols, 30% of recurrences are found outside these protocols, and only 10% of patients with recurrent disease have curable tumours.[3,4]

The search for prognostic biomarkers in RCC has led to investigations of the soluble urokinase-type plasminogen activator receptor (suPAR), a non-specific marker of systemic inflammation.[5,6] suPAR has been associated with detection and survival in various diseases, including RCC.[7-9] In this study, the authors' aim was to investigate the prognostic accuracy of pre-operative plasma suPAR in predicting recurrence and survival in patients who received curative intent treatment for localised ccRCC. The authors hypothesised that an elevated pre-operative suPAR would be correlated with poorer overall survival and recurrence-free survival.

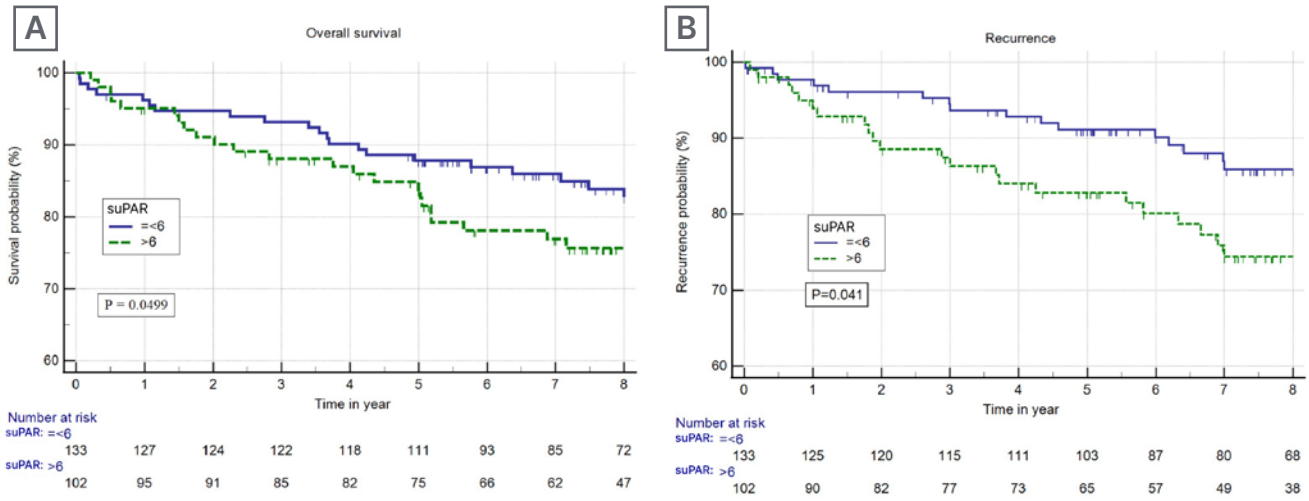
MATERIALS AND METHODS

Plasma from 235 patients with pathologically confirmed ccRCC and stored in a Danish National Biobank were identified for this study. Demographic and pathological data were extracted from patients' electronic medical records. The level of suPAR, along with other factors such as age, gender, method of treatment, T-stage, Fuhrman grade, Charlson Comorbidity Index (CCI) score, presence of hypertension, level of C-reactive protein, level of haemoglobin, and presence of symptoms were analysed. The concentration of suPAR was measured using the commercial suPARnostic® (ViroGates, Birkerød, Denmark) assay kit and analysed through spectrophotometry. Descriptive statistics and the area under the curve operator were used to indicate the overall performance of the diagnostic test of suPAR. Analyses were performed using MedCalc® Statistical Software (MedCalc, Ostend, Belgium).

RESULTS

This study included 235 patients with ccRCC. The analysis showed that pre-operative plasma suPAR levels of ≥6 ng/mL were significant negative predictors of both overall survival (hazard ratio: 1.69; 95% confidence interval [CI]: 0.99–2.89; p=0.050) and recurrence-free survival (hazard ratio: 1.91; 95% CI: 1.03–3.57; p=0.041) (Figure 1). Furthermore, suPAR levels of ≥6 ng/mL remained a negative predictor of overall survival in multiple regression analyses (odds ratio: 5.18; 95% CI: 1.50–17.93; p=0.009). The prognostic performance of suPAR was 0.576, and

Figure 1: The overall survival and recurrence-free survival rate for patients with (A) high and (B) low soluble urokinase-type plasminogen activator receptor.



SuPAR: soluble urokinase-type plasminogen activator receptor.

adding suPAR measurements did not significantly improve the diagnostic accuracy of the Leibovich scoring system, but the combination of suPAR and T-stage had the same diagnostic performance as the Leibovich scoring system alone (area under the curve: 0.735). These findings suggest that pre-operative plasma suPAR may be a useful prognostic biomarker in predicting recurrence and survival outcomes in patients with ccRCC.

CONCLUSION

This study highlights the importance of measuring suPAR as a predictive tool in the progression of RCC, identifying a two-fold difference in recurrence risk when circulating suPAR exceeds 6 ng/mL. When adjusted for the most relevant clinical and histological parameters associated with RCC, this showed for the first time that pre-operative plasma suPAR has the potential of being prognostic for recurrence and overall survival. Pending external prospective validation and standardisation, the authors see promise in suPAR as a liquid biomarker for RCC. ●

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Genomic Profiling of Urothelial Carcinoma *in Situ* of the Bladder

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Keywords: Bladder cancer, carcinoma *in situ*, exome, genomic profile, RNA, sequencing analysis.

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BACKGROUND AND AIMS

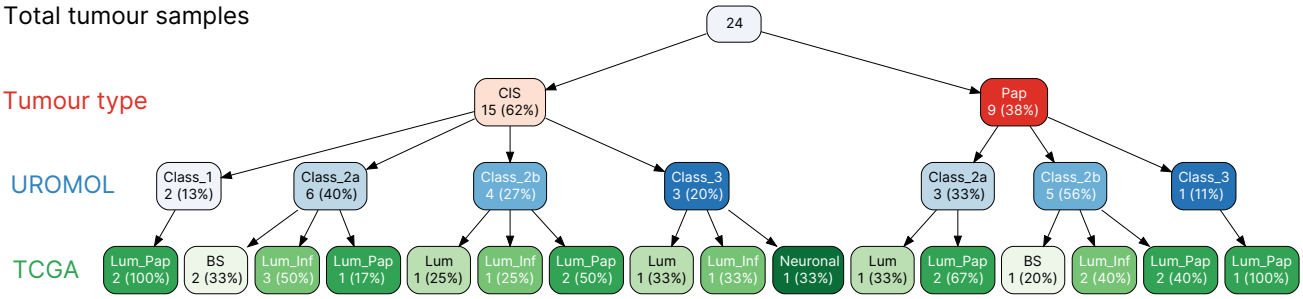
Urothelial carcinoma *in situ* (CIS) of the bladder is an intra-epithelial, high grade, malignant neoplasm characterised by flat (non-papillary) growth, with high probability of disease progression.[1,2] CIS has histologic features similar to invasive cancer and is often a precursor to and associated with invasive cancer. Molecularly, bladder cancer can be broadly categorised into luminal and basal subtypes.[1-7] However, the molecular features that are unique to CIS, as compared to other high-grade lesions, including papillary Ta and T1 tumours, are underexplored.

Bulk RNA expression profiling is a standard for molecularly characterising bladder cancer, and RNA-sequencing protocols utilising formalin-fixed paraffin-embedded (FFPE) tumours are well established. However, CIS presents challenges for RNA sequencing due to the inability to reliably detect, the low incidence rate, and the quality of RNA derived from FFPE samples. While enhanced cystoscopy and narrow band imaging have improved the ability to detect CIS, sampling acquisition techniques still limit the optimisation of RNA sequencing. Furthermore, the authors determined that established dual nucleic acid extraction protocols for FFPE samples were not feasible due to small biopsy sample sizes, and that protocols should be optimised for either RNA or DNA. This study attempts to overcome above stated challenges to understand the molecular landscape of CIS by contrasting against papillary tumours and normal urothelium using RNA-sequencing on FFPE samples, as well as whole exome sequencing, and immunohistochemical and immunofluorescent analyses, with an intent to identify unique molecular signatures associated with CIS.

MATERIALS AND METHODS

The authors performed whole transcriptome profiling with RNA sequencing of FFPE specimens from 15 CIS, nine high-grade papillary Ta/T1 tumours, and eight normal urothelial samples (Cohort A). Wilcoxon test was used to filter differentially expressed genes and The Cancer Genome Atlas (TCGA) single sample classifier was used to assign molecular subtypes. Whole exome sequencing was performed for 19 patients with matched CIS and papillary tumour samples (Cohort B). Using multiplex immunofluorescence and immunohistochemistry analyses, 24 samples from 15 patients were analysed for the presence of cytotoxic T cells, T helper cells, regulatory T cells, B cells, M1 and M2 macrophages, and programmed cell death protein 1 and programmed death-ligand 1-expressing cells.

Figure 1: The Cancer Genome Atlas and UROMOL subtyping classifier (N=24; 15 carcinomas *in situ* versus 9 papillary tumours).



BS: basal; CIS: carcinoma *in situ*; inf: infiltrated; lum: luminal; pap: papillary; TCGA: The Cancer Genome Atlas.

RESULTS

The authors performed molecular subtyping applying the UROMOL classification and as previously shown for CIS, the majority were Class 2a and 2b, with four Class 3 and one Class 1. They applied the TCGA single patient classifier and the majority were luminal with a breakdown of two luminal, five luminal infiltrated, seven luminal papillary, three basal, and one neuronal subtype (Figure 1). A 46-gene signature of differentially expressed genes in CIS samples was identified and included known druggable targets that were selectively upregulated (*MTOR*, *TYK2*, *AXIN1*, *CPT1B*, *GAK*, and *PIEZO1)* or downregulated (*BRD2* and *NDUFB2*; $p<0.05$). An independent dataset was used to assess the robustness of these markers. High expression of *MTOR*, *GUSBP11*, *KMT2D*, and *URB1* was significantly associated with CIS in this independent dataset.

Additionally, mutational analysis of 34 matched CIS and 33 papillary tumours revealed a clonal origin of the lesions with mutations shared between both synchronous and metachronous tumours. Inter- and intra-patient mutational heterogeneity was also observed. The most frequently mutated gene was *KDM6A*, which was observed in 53% of the patient samples. Analysis of the immunological landscape of 24 CIS and papillary tumour lesions showed higher levels of immune cells in stromal compartments compared to carcinoma regions. Furthermore, more programmed cell death protein 1 positive cells were observed in CIS lesions compared with papillary tumours ($p=0.03$).

CONCLUSION

Collectively, this study identifies a molecular signature that distinguishes CIS lesions from papillary tumours in terms of gene expression levels, mutational landscape, and proportion of programmed cell death protein 1 positive cells that may contribute to an aggressive feature of progressive disease phenotype of the bladder cancer.

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Congress Interview

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EAU 2023

Q1 Since you last spoke to EMJ in 2020, what have been the largest changes you have observed in the specialty of urology?

A large part of urology is uro-oncology, so let's start here. We have seen a minimalisation of surgery, so we are doing more robotic surgery and are trying to preserve more organs. For example, in renal cell cancer, we try to spare the kidney if possible and be minimally invasive. Unfortunately, we have not been able to preserve the majority of bladders with advanced disease, but we can now consider borderline indications for cystectomy with the aim to reduce this where possible. This might involve combining extensive transurethral resection with systemic therapy or physical therapies. In prostate cancer, I would say we have also been more conservative; for example, when looking at when to perform radical prostatectomies in patients who have a good prognosis. So, there is less surgery and less open surgery in oncology.

In systemic therapy, I think it is remarkable that we can use combinations of checkpoint inhibitors to produce very long lasting results in patients with renal cell cancer. Unfortunately, this is not the case in all patients, but it is really encouraging that we are seeing this more commonly. The same can be said in urothelial cancer, where checkpoint inhibitors were a new entity and did not fulfil the expectations we had. We now see a definite cure and I have patients living for several years without any metastases after metastatic disease, with or without prior surgeries. For prostate cancer, we are also observing many more years of survival in patients with very advanced disease.

In terms of non-oncological disease, there have been notable advances in surgery, like in the case of very large benign prostatic hyperplasia. This used to be a case for open surgery, but is now conducted with the help of laser enucleation and morcellation. Therefore, we are seeing more minimally invasive interventions for treating diseases that were previously deadly in oncology, and affected quality of life in non-oncology.

In research, I think that better genetic classification of oncologic disease is definitely something that is taking off. In urology, we are behind some disciplines in this regard. For example, in prostate cancer we need a better stratification of the types of treatment and the prognosis patients have, but this is a work in progress.

Q2 You spoke to us previously of your involvement bringing new colleagues into offices and committees within the European Association of Urology (EAU). What are your proudest achievements thus far in your role on the board of the EAU?

Firstly, one of the important offices is the scientific committee; a group of 25 people from all over Europe, who compose the scientific components of the annual meeting. Here, we have been able to recruit new members such as the new chairman, Peter Albers, who is an excellent researcher. He is conducting leading research into prostate cancer, including the PROBASE study, which investigates prostate-specific antigen in young males using a large, multicentre, nationwide design. The scientific committee is also doing a great job acting as a messenger for research in Europe and sharing this with all our international colleagues.

Q3 What are some of the recent challenges the EAU has faced, and are there any you have had to overcome in your role specifically?

There are always changing patterns in urology, as it is seen and practiced differently in the general population, by politicians, and by our colleagues in other fields of medicine. This carries across different countries and areas all over Europe. In the UK, for example, urologists do less uro-oncology, unless it is carried out with a multidisciplinary board. In contrast, systemic therapy is conducted across many departments and in many areas within urology in Germany. Another difference might be neoadjuvant chemotherapy prior to a cystectomy, for example, specifically whether this is performed with the help of the oncologist or completed by the oncologist in their own department. In some hospitals and institutions this

means the patient is moved through different departments and this can be a little more complicated, making communication very important. There are advantages and disadvantages, and this is one example of problems we discuss.

"There are always changing patterns in urology, as it is seen and practiced differently in the general population, by politicians, and by our colleagues in other fields of medicine."

We have also had to deal with Europe in a geographical and political way. There are several important countries outside of the European Union (EU), and some are involved in war at the moment. This is difficult, but we are a scientific and professional association and as such, we cannot, should not, and must not deal with any politics. But this can be a real challenge, and there are associated administrative problems. As a research association, we have strictly maintained our goal of fostering the field of urology for the benefit of patients, irrespective of any political issues.

Another challenge we are facing relates to how, in most countries in Europe, more females are going into urology. At my university, 75% of all medical students and half of our residents are female. Yet out of six staff members, only one is female. Not all but some females tend to reduce their workload after they finish their residency, meaning they move away from the clinic into office urology. In the future, we will have to tackle how to motivate our female colleagues to go into research or to stay in the clinic. This has a large impact on the EAU as well. Working

part-time, they may join a regional organisation but might not become members of an international association.

Q4 What are the key messages and themes to watch out for at the EAU23 congress?

Well, there are several. One is showing how minimal we can be with surgical interventions. The advantages of systemic therapy are related to this, with better selection of these therapies. Another key message is early detection. In the last few months we have adopted a new policy involving urology. Europe's Beating Cancer Plan provides better funding for research and the implementation of early detection of cancer. This explicitly includes prostate cancer as one of the specific cancer types for this programme.
I know there is a lot of discussion about screening, and this is an important question. We are no longer talking about just taking blood from a patient, performing a biopsy, and then surgery. There has been significant progress regarding the inclusion of imaging, so as to avoid unnecessary biopsies, and to better identify prognostically unfavourable cancers. This also helps decide which patients should be moved to active surveillance. There are new strategies, which do not only include blood tests and MRI, but substitute MRI with micro-ultrasound, artificial neural network, or artificial intelligence with ultrasound for a better correlation with prostate-specific antigen. There are now messenger RNA tests that can be combined with image theorems for early detection.

All of this aims to minimise psychological and physical disadvantages for patients, while of course avoiding poor outcomes such as death from metastatic prostate cancer, or paralysis due to bone metastasis to the vertical column.

Q5 Where can we expect to see your research and education focus in the near future?

My particular interest is in patient-derived organoids, and this is really personalised medicine. This technique, which involves taking tissue from patients and developing patient-derived organoids, shows promise for the future. These can be used in research and in testing individualised responses to a possible treatment. We have tissue to work with, and can see how different drugs might work. Later you might take a biopsy and find that another drug is more suitable, or that the same treatment is working but requires adaptation of dosage. Primary cultures have already been tried, but the use of organoids is a better way of including epigenetic aspects and the issues that may arise with tumours.

There is also a major project going on, funded by several million euros, investigating the use of sensors that provide real-time information about the composition of a tissue during surgery. This might help classify a tumour as either benign or malignant, and could help identify nerves and vessels to avoid major complications or loss to quality of life. Fortunately, we have the funding for this, and it is of course something we must do in collaboration with bio-scientists and engineers.

Q6 Are there any topics in the field of urology that you feel require greater attention, and on the contrary are there any recent advances that you think show great potential?

I wanted to mention endourology, as this is a really important aspect in our specialty. In endourology there is a lot of focus on infertility treatments that, in some parts of the world, is very necessary. In Denmark there is a very strong group working on fertilisation with testicular tissue, specifically focusing on how we can use this tissue to improve the treatment of infertility.

Interviews

The following interviews take a look at the future of urology, by exploring the impressive careers and experiences of numerous experts. Interviews with several leaders in the field are included, who speak about topics ranging from robotic partial nephroctomy to nocturia and overactive bladder.

Featuring: Ben Challacombe, Juan Gómez Rivas, Kari Tikkinen, Bhaskar Somani, and Timothy Clinton.

Ben Challacombe

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Q1 Having spent over 10 years in your current role with Guy's and St Thomas', what initially sparked your interest in urology and has pushed you to reach your established position today?

The interview answer to why most people do urology is probably similar to the real answer for me; it's a specialty which deals with quite common diseases of ageing, but it does deal with both males and females, and can range from very small procedures all the way up to quite massive operations. I've been involved with quite a lot of cancer work, which I find very stimulating, and I suppose within all that there has been a link with urology.

This specialty has been very good at being an early adopter and embracer of technology. Most of the things I do are either with robotics or with laser technology, and I think that has kept it really exciting for me over the over the 10 or 12 years in which I have been consulting.

> **"You need to learn from others, yourself, mistakes, rare complications, every day and every week."**

Q2 As the highest-volume surgeon for robotic partial nephrectomy in the UK, what are some of the unique challenges associated with performing this type of procedure?

In robotics, I do about half kidney and half prostate procedures. For me, the kidney provides a real variety that is very exciting; you can get a tumour on the left kidney or the right kidney, you can get it on the front or the back, it can be sticking out, it can be sticking in, it can be small or medium or large... So you have to do a lot of kidney surgeries before you find two procedures that are exactly the same. All of these different situations mean that there's so much variety, and I find that very stimulating.

However, the prostate is a much more standardised procedure. The steps are very precise, and you could almost write these down for every operation. The challenge here is that it's so complicated. With prostate surgery you never get it absolutely perfect, and you're always searching for a sort of 'holy grail' and the perfect operation. Even when you get it 98% right, in your own mind you're thinking, "Maybe I could have got a couple more percent." I think those for me complement one another; one is the variety of cases, and the other is the challenge of delivering an excellent procedure every time.

Q3 How does leading a HIT list surgery differ to usual procedures? In what way do you see this initiative impacting the field of urological surgery in the near future?

I picked up on the HIT list program after seeing publicity from some other specialties. Being a surgeon, and therefore relatively competitive, I thought, "Why can't we do some? Can we get involved in urology?" It's pretty difficult to do within the NHS, to produce an incredibly rapid turnover and absolutely maximise the time surgery is taking place within the operating theatre. When you divide a surgeon's time up, less than half of their day will be actually

performing surgery in theatre, and there is a lot of downtime, waiting before and after cases. The concept feeds right into surgeons' hands, who love operating and want to do the job they have been trained for, minimising any delays and interruption. It really is a concept that can be applied across all surgeries in our, and every other, department.

Leading the surgery, there was an element of bringing everybody on board, and getting everyone enthused. This was pretty easy in an environment where people like a challenge. There were so many people involved in this, with multiple teams meeting together and on Zoom calls, from the nurses on the ward to recovery, pharmacy, and nurses in the clinic.

I may be biased, but I think this was the most complex HIT list we have done. For example, if you're just operating on hernias, the patient comes in for their procedure and they go home on the same day; whereas with cancer surgery using catheters, you've got to prepare the patient beforehand, you've got to deliver a surgery, and then they need quite a lot of follow-up in those first couple of weeks.

We had to get the timetable prepared, and we had to organise the consenting process from an anesthetic and the surgery point of view beforehand, so that the patients could come in in a streamlined manner on the day. All of the preparation was done upfront, and this allowed us to really knock through the work on the day. This could only happen because of all the time and effort put in to organise it beforehand. It worked really well.

Q4 Having collaborated on over 200 peer-reviewed papers, multiple book chapters, and more than 400 presentations, are there any gaps in the literature within your specialty you would like to see more research?

There are gaps that have never been answered that should have been. But there are also new gaps emerging. So, if we get a new type of robot, like we did last year, we can look at how this compares to an existing robot, and this is new research. We may well be getting another new robot soon, so then there will be work comparing all three. But then I suppose there are also those moments when you sit at home or lie in bed with a cup of tea and think, "Well, why has nobody ever looked at that?"

Touching on the HIT list again, it's made us think about some of the processes we do as standard, and whether we really need to do them that way. We ask questions like, "Why can't we have an turnover of 10 minutes on an average day?" In our case, we have found the patients themselves started supporting each other, forming a WhatsApp group to talk about milestones, and comparing recovery. There are some amazing things we can take away from this initiative, for me the most important being the enthusiasm and energy it provided.

You can only change two things in a fixed system within the NHS: efficiency and morale. Everything else is fixed; a certain amount of days, a certain amount of theatre time, and so on. We managed to affect morale in order to improve efficiency, with exactly the same footprint of kits, equipment, and personnel. In terms of tangible research, we have written this all up and there will be some papers coming soon; that in itself it is a new niche.

> **"This specialty has been very good at being an early adopter and embracer of technology."**

Q5 Your education and professional experience have involved you travelling as far as the Royal Melbourne Hospital in Australia. Where do you believe you gained the most valuable experience, and how was this integral for you to make it to where you are today?

Firstly, you're learning all the time, and anybody who thinks they aren't shouldn't be doing surgery. You need to learn from others, yourself, mistakes, rare complications, every day and every week.

The seminal year of my life, in terms of crossover between experience and learning, was my year in Australia. You're exposed to a completely different situation in another healthcare system. You see how people handle themselves, and what they do, good and bad. This actually stimulated me to run our Fellowship programme, and the Fellows turn up thinking that they are here to be taught by me. But I am as equally interested in what they can tell me about where they come from, and what they do in different ways. We hear from them in our academic meetings, asking them to tell us all the things they do that we can improve, so we can all learn as a department.

That is the key year as a young surgeon, that final year of training. After that, no one really trains you, and you have to sort of fend for yourself. I would advise that if you can, and it works with your family and your partner, do a period of time abroad, as it is a very valuable experience.

Juan Gómez Rivas

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Q1 Why did you decide to pursue a career in urology, and what continues to motivate you today?

Urology is one of the medical specialties with the highest involvement in new technologies. From endoscopic surgery to laparoscopic robot-assisted surgery, we are one of the leaders in disruptive technologies in the medical field. Also, urology combines surgical with clinical-medical activity, covering many subtopics from benign diseases to oncology. My field of interest is genitourinary tumours. Lately there has been a big change in the management of genitourinary tumours, with novel drugs, targeting agents, and tailored medicine. Nowadays, motivation in the clinical aspect comes from patient satisfaction, and for the academic part, in leading a team of young and enthusiastic people and pushing forward to increase the academic level in Europe. This team is the Young Academics Urologists (YAU) of the European Association of Urology (EAU).[1]

Q2 What experience did you gain from your role as Chairman of the European Society of Residents in Urology (ESRU), and are there any notable achievements that come to mind from your time in this position?

I was part of the ESRU for 5 years, and I learned multiple soft skills such as leadership, communication, and teamwork. In these 5 years, we published many papers about the actual status of urology training in Europe, raising awareness of the lack of confidence, lack of training in major surgery, and amount of surgical simulators, among others. Also, we found that although the residents present their work at congresses, this does not translate into scientific publications, so there is a lack of academic-scientific motivation, and it mainly depends on going abroad or getting into a PhD programme. Nowadays, the EAU is working hard to make urological education reachable at all levels in Europe.

Q3 Having participated in multiple international congresses and collaborated on more than 250 published scientific papers, what will you be focusing on next as an educator?

The natural pathway of doctors should be to achieve proficiency in their field of interest, and deliver this knowledge to the next generations. In the YAU, we are working on building an open academic curriculum for everyone. This curriculum should be Pan-European, unbiased, and high-level, covering the latest updates in research, and led by experts.

Q4 Drawing upon your experience as a clinical observer, are there any innovations on the horizon in the fields of laparoscopy and focal therapy techniques for prostate cancer?

Prostate cancer is living a revolution in terms of diagnosis and treatment. There are novel imaging techniques such

as MRI, prostate-specific membrane antigen, and micro-ultrasound, among others, which allow us to see, diagnose, and control a tumour that we were not able to see a few decades ago. Focal therapy and robotic surgery allow us to deliver tailored treatments with good oncological results, without harbouring the quality of life. New energies to deploy inside the prostate are coming, and new robots are in the field, so the future is promising.

"Lately there has been a big change in the management of genitourinary tumours, with novel drugs, targeting agents, and tailored medicine."

Q5 How is the EAU, with whom you have several positions of involvement, educating healthcare professionals and trainees in the field of urology?

The EAU offers numerous resources and programmes for optimal learning in urology for doctors at any stage of their urological careers. The educational arm of the EAU is the European School of Urology (ESU). The ESU aims to stimulate, coordinate, and organise all postgraduate teaching and education activities of the EAU at the highest level possible. Therefore, all teaching activities organised by the ESU are open to constant evaluation. No matter what stage you are in your career, the EAU-ESU can offer you valuable learning resources, designed to prepare the frontrunners in urology, including masterclasses, courses, hands-on training, webinars, on-demand activities, e-courses, and podcasts, among others. There are educational platforms with the latest findings on clinical trials, insights from meeting reports, and interviews with key opinion leaders called UROONCO[2] and UROLUTS.[3] Furthermore, urologists can be part of scholarships and exchange programmes at reputable European institutions from an early stage, and team up with experts in clinical and experimental research via the European Urological Scholarship Programme (EUSP).

Q6 You recently co-authored the study, 'Augmented reality' applications in urology: a systematic review'. What were the key findings from this investigation?

Augmented reality applied to surgical procedures refers to the superimposition of pre-operative or intraoperative images into the operative field. Augmented reality has been increasingly used in a myriad of surgical specialties, including urology, and its advances have led to increasing registration accuracy, as well as increased ability to identify anatomic landmarks, and improve outcomes during urologic procedures, such as robot assisted radical prostatectomy and partial nephrectomy.

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Kari Tikkinen

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Q1 What initially sparked your interest in medicine, and what led you specifically to the field of urology?

I was not sure about medicine until I was almost 20. In high school I was thinking, besides medicine, about biology, geography, and sports for university. I ended up with the most "secure" one, and I have not regretted that. Life probably would have been quite different if I had chosen something else.

In medical school, I was always interested in both medicine and surgery. I don't think that is very typical. I think many medicine students are clearly thinking that I definitely want, or I definitely don't want, to become a surgeon, and the same applies for internal medicine for many of those who become surgeons. But I was genuinely interested in both. I found that urology and cardiology were fields that were in between surgery and medicine, urology being the most conservative field of surgery, and cardiology the most interventional field of medicine. But despite being the most conservative, I found many fascinating surgeries and interventions in urology.

I went to medical school at the University of Tampere, Finland. Urologic research was one of the strongest fields there. At the end of medical school, I started to work on my PhD on nocturia and overactive bladder, supervised by urology professor Teuvo Tammela and epidemiology professor Anssi Auvinen. I felt that I somehow understood lower urinary tract symptom research, and felt that I could contribute a little bit. I also met many urologists that were the nicest colleagues possible. So, urology was then a logical choice for me. And again, I have no reason to regret. Urology is indeed a great field. I really enjoy the patient interaction and follow-up of patients that is more common in urology than in general in other surgical fields.

Q2 How do you balance your work as a Professor and Supervisor at the University of Helsinki alongside your surgical roles?

I was appointed as Full Professor of Urology at the University of Helsinki in June 2020. Earlier, I worked for many years as 75% clinician and 25% Academy of Finland clinical researcher. In reality, as is typical for clinician-scientists, that 25% researcher portion took substantially more hours than you would get from 25%. Since being a Professor, I have been less involved in clinical work. But I find it important and interesting to continue in clinical patient work. Currently, I work about 35% in clinical work and 65% in research. Of my clinical work, one-third is operations, mostly endourology, one-third is outpatients, including some smaller operations, and one-third is mostly urodynamics. I only do a small variety of operations to maintain or improve the quality in those.

Most of my time as Professor, I do research. But what is it in reality? The

type of research we do; large-scale, randomised trials and meta-analyses with pragmatic approaches and patient-important outcomes, is, unfortunately, undervalued, and not so well financially supported in Finland. So, for a big proportion of my time, I apply for grants to keep our projects alive. The rest of the time, I oversee projects, plan new ones, guide postdoc and PhD students, and write; I really like those tasks.

I also have positions at the scientific committees of the European Association of Urology (EAU) and International Continence Society (ICS), different guideline groups, *Scandinavian Journal of Surgery*, and at some Finnish governmental institutes. Different kinds of tasks for these endeavours also take time. I also give some lectures for medical students and other doctors. So, I am not suffering from lack of work.

Q3 You are the lead of the Clinical Urology and Epidemiology (CLUE) Working Group. Could you discuss the aims of this group, and how it came into being?

During my post-doctoral fellowship at McMaster University, Ontario, Canada, hosted by Distinguished Professor Gordon Guyatt, I was exposed to the cutting edge of evidence-based medicine, and learned advanced methods of clinical epidemiology. The fellowship inspired me to recruit Finnish and international collaborators to create a collaborative research network, the CLUE Working Group. We work on a range of projects at the forefront of clinical epidemiology. We aim to deliver improvements in our understanding of disease management across urology and other areas of surgery and medicine. CLUE includes numerous clinicians and methodologists with a shared vision of promoting evidence-based clinical practice through practice-changing research, innovation in research methodology, and the promotion of evidence-based medicine practices and education, as well as knowledge translation. We have conducted numerous large-scale series of systematic reviews and meta-analyses, as well as large, pragmatic, randomised trials. We are just revising ethics and drug regulator applications of the Avoiding Risks of Thrombosis and bleeding in Surgery (ARTS) trial that is going to recruit more than 5,000 patients undergoing urologic, general, or gynaecologic surgery. The ARTS trial will be the first to compare the

direct oral anticoagulant apixaban to no anticoagulation in these fields. This study has potential to change practice towards more patient-friendly and effective approach worldwide.

Q4 You have extensively researched population studies of lower urinary tract symptoms, particularly nocturia and overactive bladder. Your PhD thesis on this topic achieved international recognition. Could you discuss your findings, and the importance of this topic?

My PhD thesis was based on the Finnish National Nocturia and Overactive Bladder (FINNO) Study. We invited a random sample of 6,000 Finnish men and women aged 18–79. Approximately two-thirds participated; a big thanks to all of them! In the population-representative FINNO Study, approximately 28% of subjects reported one, 10% two, 2% three, and 1% four or more void(s)/night. Nocturia was more common among young females than young males, but more common among males than females in old age. Most subjects reported small bother from nocturia with two nocturia episodes, and moderate bother only from three nocturia episodes. Two nocturia episodes impaired health-related quality of life compared to those with no nocturia. We found several important risk factors for nocturia, highlighting its multifactorial aetiology.

We also studied so-called overactive bladder syndrome. We found that the prevalence of overactive bladder was 6.5% for males and 9.3% for females, i.e., approximately half of that reported in earlier studies. We found that in the earlier literature, many methodological flaws had led to overestimation of prevalence estimates. For me personally, this part of the thesis led to understanding how important the definitions of diseases can be. If we are not careful in using definitions, we can easily overdiagnose and overtreat, or underdiagnose and undertreat, conditions. Many current definitions of diseases are leading to the overuse of scarce resources in healthcare systems.

Q5 You chaired the European Association of Urology (EAU) Guideline on Thromboprophylaxis in Urological Surgery, published in 2017. This was the first specific surgical thromboprophylaxis guideline, which holds a great deal of potential in clinical practice. How did you come up with this guideline, and why is it so important?

I did my 3-year postdoc at McMaster University between 2011–2013. I had also started as guideline member of the EAU guideline of male lower urinary tract symptoms, so I knew some of the EAU guideline leaders. At McMaster we started to do research on thromboprophylaxis of surgical/urologic patients. EAU leaders asked my opinion if we should have an EAU thromboprophylaxis guideline. I thought not necessarily, as other guidelines were so large and so urology-specific, such as prostate cancer, kidney cancer, or male lower urinary tract symptoms, that thromboprophylaxis felt somewhat small compared to them.

Despite this comment, about year later, I was asked to chair the guideline. I collected a great group, and we started to work hard. We wanted to do it properly, and that is why it took about 4 years. The first step was to establish procedure-specific risk of thrombosis and bleeding. This had never been done in any field of surgery before. After this massive amount of work, the project that we call ROTBUS (procedure-specific risks of thrombosis and bleeding in urologic surgery), we were

> **"If we are not careful in using definitions, we can easily overdiagnose and overtreat, or underdiagnose and undertreat, conditions."**

able to provide that first ever procedure specific guideline of thromboprophylaxis in any field of surgery.

This work has been very rewarding, and important for patients. We just finalised a similar kind of work for more than 100 general abdominal and gynaecologic surgery procedures, and are starting a large pragmatic trial that examines apixaban in urologic, general abdominal, and gynaecologic surgery patients. We welcome centres to join this potentially very practice-changing ARTS trial by contacting me.

Q6 You are National Principal Investigator of the SOLIDARITY trial on COVID-19 treatments, led by the World Health Organization (WHO). Please let us know the aims of this trial, and any important findings to date.

When the COVID-19 pandemic started, I saw that clinicians were increasingly using hydroxychloroquine and other experimental treatments without trustworthy evidence. I felt that I had to do something. I had trial leadership experience from leading the Antibiotic Prophylaxis Before Shock Wave Lithotripsy (APPEAL) trial; we recently completed the recruitment of more than 1,600 patients and are analysing the data. So, I tried to start a COVID-19 trial in Finland, and was finally able to convince some folks to work together.

In the end, as part of the global WHO Solidarity trial, we were able to launch a nationwide, randomised trial that included all university hospitals, and many other major hospitals in Finland. We first studied remdesivir, and are currently studying imatinib and infliximab. I expect we will stop recruitment during the upcoming months, as the pandemic is not as prevalent. We have so far found that remdesivir decreased mortality in COVID patients, and the earlier you start, the better. We are still not sure of the effects of imatinib or infliximab. In Finland, we also follow up all these patients for 2 years post-hospitalisation regarding recovery and potential long-COVID symptoms.

I am very glad that we were able to launch SOLIDARITY Finland. Besides providing high-quality evidence for future patients, we have learned a lot about how to conduct large, pragmatic global trials.

Q7 As an educator, what are you working on at the moment? Where will your focus will lie in future?

Teaching young colleagues is a privilege. I hope I can continue contributing through teaching and studying how to diagnose and treat urologic patients and beyond. For me, it is important that we conduct more high-quality research so that we know better what to do. We also need to include peoples' values and preferences in the decision-making process. With all our technical and scientific advancements and increasing commercialisation, there is risk that physicians forget, or don't have time, to provide kind care for our patients. These issues are very important, and I will keep educating about them. In terms of research, I am constantly struggling to get funding for this kind of patient-centred, evidence-based research in Finland. But I will keep my eyes open for all opportunities.

Bhaskar Somani

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Q1 What led you to pursue a career in surgical urology? Was there a particular person or event that inspired you?

As a junior doctor in training, I enjoyed all aspects of surgery, having done specialist vascular surgery, thoracic surgery, orthopaedics, general surgery, and urology jobs. I found urologists very nice and humble, and easy to work with. There was also such a huge spectrum of choice in urology, with laparoscopy, endourology, andrology, and functional urology, with robotic surgery on the horizon at the time. Urology was a no-brainer for me really, like a big family, and I have never looked back since choosing it.

Q2 You currently have over 500 peer-reviewed papers, more than 550 abstracts, and multiple book chapters published on a range of topics from benign prostate disorders to haematuria to stones. Where can we expect to see your focus lie in the coming years?

God has been very kind to me, and I have worked with some great researchers, colleagues, and juniors. Most of my ideas and collaborative projects have been published due to the hard work and commitment shown by the whole team. We now have three endourology Fellows, and our 'Stone Team' has grown from one (which was just me in 2012) to 12 in 2023, which shows our success as a team.

Going forwards, besides endourology, I am increasingly involved with novel stents and catheters, non-antibiotic treatments for simple and complex urinary tract infections (UTI), minimally invasive surgical therapies (MIST) for benign prostatic hyperplasia (BPH), artificial intelligence (AI), and machine learning (ML), with predictive models for different urological conditions. I think we really need to invest in these technological innovations to help our patients.

Q3 What do you believe to be the current gaps in urological literature, and which topics merit greater attention?

There are several areas of urology which are rapidly changing and evolving. I do feel that we still need novel oncological therapies which can minimise the use of some morbid surgical procedures; better suction devices after stone treatment to prevent recurrences; ideal MIST treatment and algorithm for BPH; and better diagnostic and predictive tools using AI and ML. But there are several areas of urology where patient involvement, patient-reported outcome measure (PROM), and cost effectives need to be addressed.

Q4 You were involved in pioneering a technique called 'pop-dusting' to remove kidney stones. Are there any exciting new procedures you are aware of that are emerging in the field of surgical urology?

We are proud with our results of 'pop-dusting', and recently have shown its use

in large and multiple stones using the high-power laser. Patients avoid more invasive or second surgical stone-related procedures using this, and we have shown its use in both adult and paediatric patients.

Of the new areas, multiple new MIST for BPH are coming through. This is a whole new technological rainbow, which is constantly evolving and offering a plethora of choices to patients and clinicians alike. There will be the increasing role of mobile phone apps, new robots, and lasers in the next few years. Personalised medicine, perhaps with the increasing role of genomics, is also likely to be more commonly used in future.

Q5 Being listed as the number one surgeon in the world for ureteroscopy and keyhole percutaneous stone procedures, can you describe some of the unique challenges associated with these patients?

I am slightly uneasy in taking about the numbers, as there are many surgeons who are more skilled than me, and some of them are my mentors in this field. I consider myself lucky to have been trained by, and to be working and collaborating with many of these urology colleagues, who are all excellent in this field.

The challenges of stone surgery are related to primary and recurrence prevention. Unfortunately, although the surgical aspects of endourology have become more modern and minimally invasive, we need to do more in terms of prevention of stone disease. Recently, the European Association of Urology (EAU) guidelines have updated the follow-up guidelines, and recommend more intense follow-up for these patients, as many of them recur in time. This is also something we will need to apply in our clinical practice for recurrence recognition, counselling, and treatment.

Some of the other challenges related to these surgeries are better operative monitoring of intrarenal pressure and temperature during these procedures.

"Urology was a no-brainer for me really, like a big family, and I have never looked back since choosing it."

Equally, application of AI and having better predictive tools, or using it during surgery, can possibly improve the overall clinical outcomes.

Q6 What are the most significant changes you have seen in the field of endourology over the course of your career?

There are so many changes I have witnessed which have made endourology safer, less invasive, and a sub-specialty that appeals to most trainees as a career choice. I guess the journey started with flexible ureteroscopes, which then changed from fiberoptic to digital scopes, and is gradually now evolving with digital disposable scopes, which either are much smaller or smarter with pressure monitoring. Similarly, in the field of lasers, the use of high-power laser, pulse modulation of holmium laser, and now thulium fiber laser are all helping to push the boundaries of stone surgery. In the field of percutaneous surgery, there has been significant minimisation of the tract used, with more studies reporting on suction to improve the stone-free rate, and new fragmentation/suction devices to help with this. In our personal series, we have used AI and ML for predictive modelling in percutaneous procedures, patients who had urosepsis post-ureteroscopy, and a few other areas of endourology. We think these will also have a huge impact in future.

Q7 You have been involved in a portfolio of activities to promote public awareness of urological conditions. Are there any areas that require greater attention you would like to spotlight here?

I have been involved with several aspects of primary prevention of stone disease. More work needs to be done around antimicrobial resistance and the use of non-antibiotic therapies for simple and complex UTIs. Similarly, the roles of fluid intake, obesity, hypertension, and diabetes need to be highlighted for these patients, and more patient awareness and education is needed.

Q8 What are some points of emphasis you incorporate into practice that an aspiring urologist could use to be the best they can be?

There are several aspects of urology that I have enjoyed. With several sub-specialties offered, they should choose the specialty that most appeals to them rather than going for the most popular choice. I would also suggest they have some research and academic or teaching role along with their clinical work, which makes them more accomplished as a clinician. Having a good work-life balance, and engaging in regional, national, or international activities would make the whole journey more enjoyable.

During my own journey, I have had a mixture of clinical research, teaching, and training with the European School of Urology (ESU), papers and grants, EAU guideline panel, and EAU section(s) work. These, combined with innovative clinical work, have made me a more complete surgeon. Finally, please enjoy this journey, which will be more special in what you enjoy and with the team you want to work with.

"There are so many changes I have witnessed which have made endourology safer, less invasive, and a sub-specialty that appeals to most trainees as a career choice."

Timothy Clinton

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Q1 What has driven you to specialise in urologic oncology, in particular the management of advanced testicular and bladder malignancies?

My interest in urology started in medical school at the University of Texas Health Science Center in San Antonio, USA. During that time, I learned so much about urology, but really found the surgical management of bladder cancer (radical cystectomy) and testicular cancer (retroperitoneal lymph node dissection) to be the most interesting. While they are two very different disease processes with very different survival rates, what I have always found most interesting is the vital role that appropriate surgical management plays within each disease. While surgery is one aspect of urologic oncology, what I appreciate most is the multidisciplinary approach, and caring for these complex patients as a team.

Q2 You were recently acknowledged with an award for your contributions as a peer-reviewer for urology articles. Could you outline the areas you would like to read more research in in the near future?

As a reviewer, I truly enjoy this as a means of keeping up with the constant amount of urologic research that is coming out. My personal interests match my clinical and research interests, mainly around translational research and clinical trials for bladder and testicular cancer. Whilst translational genomics research has long been centered around DNA and RNA sequencing, I am currently exploring more epigenetic changes and markers, and the emerging field of fragmentomics for cell-free DNA (cfDNA).

Q3 Part of your research interests lie with defining the genomic determinants and biomarkers of urothelial carcinoma and germ cell tumours. Are there any recent notable advances you would like to share in this field?

Recently there have been many clinical advances and large-scale genomic sequencing efforts in the management of urothelial carcinoma, but unlike lung cancer, the ability for personalised precision oncology in bladder cancer has not yet been achieved. Largely, the lack of adequate biomarkers continues to be a major deficit in achieving personalised treatment for these patients. From emerging data on circulating tumour DNA (ctDNA), and my own work in cfDNA, we are starting to see evidence for more plasma-based biomarkers. New urine ctDNA assays are emerging, and may be even better for localised bladder cancer decision-making. In germ cell tumors, the groups that have helped to identify and now utilise *microRNA-371a-3p* as a biomarker in prospective multi-institutional trials have truly moved this field forward, which has not seen much development for many years. I believe that this is just the start of a more personalised medicine approach for our patients with testicular cancer, and I look forward to the arrival of other biomarkers in development.

Q4 You recently co-authored an article, 'Genomic heterogeneity as a barrier to precision oncology in urothelial cancer'. What was the key message delivered here?

This was a project that truly took a massive effort, led by my former lab mentor David Solit, with the help of many collaborators, including co-author Jessica Chen. Utilising the large-scale sequencing effort from Memorial Sloan Kettering Cancer Centre, New York, USA, we sought to determine the degree of heterogeneity in bladder cancer by comparing mutational frequencies across grade and stage. This led to using whole exome sequencing to look at mutational concordance between primary and metastatic tumors within individual patients. This demonstrated, through phylogenic analysis, that bladder cancer is characterised by early branched evolution. Additionally, discordant *ARID1A* alterations were found only in the metastatic lesions, which suggests its role in metastatic progression. Further validation of our matched pair analysis in 119 primary/metastatic pairs demonstrated that primary and metastatic sites have 23% discordance in actionable genomic alterations. Finally, evaluation of plasma cfDNA, compared to tumour samples in 123 patients, found that 17% of targetable alterations were exclusive to cfDNA only, and 23% were exclusive to tumour samples. To summarise, in patients with progression we recommend not only metastatic biopsies, but utilisation of plasma cfDNA for identification of targetable alterations.

Q5 Having featured on a podcast recently discussing bacillus Calmette–Guérin (BCG) refractory non-muscle invasive bladder cancer, what were the key points from this session, and can we expect to see you contribute more research and discussion in this field soon?

It was a real pleasure to talk with experts Aditya Bagrodia and Eugene Pietzak about BCG-unresponsive non-muscle invasive bladder cancer. We were able to highlight the different options available for these patients, and the counselling that we incorporate with our patients in this difficult clinical scenario. My personal research in this area is looking to evaluate novel therapeutics as alternative treatment options. We know that certain alterations are associated with BCG unresponsive disease and thus, if we can target these alterations, this may be a viable alternative to cystectomy in many patients.

Q6 Robotic surgery has an increasing role in urology. How have you seen this change over the course of your career so far? Is there room for artificial intelligence (AI) in urologic oncology?

At this point, robotic minimally invasive surgery is a mainstay in the treatment of nearly every urologic cancer surgery. As a younger attending doctor, I have been trained by true experts in open and robotic surgery, and have come to appreciate the benefits and need for both approaches for the benefit of my own patients. As a surgeon most interested in bladder cancer and testicular cancer, the use of robotic surgery is emerging in both of these spaces.

I have found that in appropriately selected patients, the use of robotic cystectomy with intracorporeal diversion and robotic retroperitoneal lymph node dissection has truly been revolutionary in the recovery of such morbid operations. This truly provides a unique surgical approach for our cancer centre, and decreases pain, blood loss, and recovery. With that being said, there are plenty of patients where an open approach is still required, and additionally, robotic surgery does not negate a poor lymph node dissection or poor surgical excision. Thus, it is imperative for those of us performing such robotic surgeries to still uphold the same level of expertise as previously achieved in open surgery. The use of AI in urologic oncology will continue to grow, as we have seen already in pathology and radiology. It is only a matter of time until surgical approaches, and specifically robotic surgery, will start to include shades of AI.

Q7 What advice would you give a younger self, looking to establish themself as a clinician and researcher?

I would consider myself still a growing clinician and researcher, and at the start of my career. In general, when I counsel residents and medical students, I remind everyone that the patient remains our sole focus. There are no shortcuts in surgery, and it is imperative to understand not only the disease process and management, but the experience of seeing and learning, and ultimately mastering an operation. This learning never ends, and there are unique scenarios that will continue to challenge every clinician. As long as all of us starting our career remember thiss, I think we can all achieve success.

"It is only a matter of time until surgical approaches, and specifically robotic surgery, will start to include shades of AI."

Q8 Since your appointment at Brigham and Women's Hospital, what has been your proudest achievement? Is there anything this hospital approaches well that you think other organisations could learn from?

Brigham and Women's Hospital and Dana–Farber Cancer Institute has a unique position as a premier cancer institute; thus, our greatest approach is the ability to provide complex and comprehensive multidisciplinary care to our patients. What I find most enjoyable is engaging not only my colleagues in urology, but those in medical and radiation oncology to determine the best treatment course. My proudest achievements have been the ability to bring new techniques to the treatment of our patients with bladder and testicular cancer.

A Short Overview on Therapeutic Biomarkers for Muscle Invasive Bladder Carcinoma

Editor's Pick

In this review, the authors summarise concepts of the molecular pathways for bladder carcinomas and molecular biomarkers for potential treatment targets in urothelial bladder cancer. New therapeutic agents that have potential for treatment are discussed.

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Abstract

Urothelial carcinoma (UC) is the second most common urologic malignancy after prostatic adenocarcinoma. UC comprises more than 90% of urinary bladder tumours. The intense research involving the different molecular aspects of bladder malignancies offers potential opportunities to improve understanding of bladder cancer biology; helps to identify disease earlier; and improves prediction of outcomes or helps targeted therapy.

This review highlights the general concepts of the molecular features: molecular pathways for bladder carcinomas and molecular biomarkers for potential treatment targets in UC of the bladder. This discussion could improve the understating of pathogenesis as well as will provide new therapeutic modules, e.g., targeted therapy.

This article is a review of bladder cancer genetics, focusing on molecular changes and their significance in the pathogenesis and progression of muscle invasive UC. Also, the relevant genetic biomarkers and their products, and new therapeutic targets and agents that are being developed are presented here.

Key Points

1. Molecular technologies have facilitated the identification of bladder cancer genetics and molecular changes, and their significance in the pathogenesis and progression of muscle invasive urothelial carcinoma. The relevant genetic biomarkers and their products, new therapeutic targets and agents, and potential future perspectives are discussed in this article.

2. Biomarkers such as serum vascular endothelial growth factor, circulating tumour cells, and defects in DNA damage repair genes can predict responses to cisplatin-based neoadjuvant chemotherapy in many patients with muscle invasive bladder cancer.

3. High tumour mutational burden has been associated with response to immune checkpoint inhibitors in a metastatic bladder cancer setting. Immune checkpoint inhibitors in the neoadjuvant setting, using pembrolizumab or atezolizumab before radical cystectomy in patients with muscle invasive bladder cancer, is an approach that is in continuous evolution and needs frequent updates.

INTRODUCTION

Bladder cancer (BC) is the fourth most common malignancy in males and shows high prevalence and mortality rates worldwide despite improvements in its management.[1,2] Although non-muscle invasive BC is the commonest type, 25–30% of bladder tumours are muscle invasive (MIBC) at the time of diagnosis, and these patients often have a poor prognosis despite traditional treatments.[3] Therefore, both in treatment and follow-up, BC remains a challenging disease for urologists. Identifying promising molecular markers and improving the clinical strategies for managing BC have become crucial.[4]

Histopathological and molecular studies indicate that urothelial carcinomas (UC) follow two different molecular pathways with distinct biological behaviour. UC has two subtypes. One is the papillary, low-grade, non-invasive UC (70%), arising from urothelial papilloma or hyperplasia and have high recurrence rate. The second subtype is muscle invasive UC (Stages pT2–pT4) that often develops metastases, and 5-year survival rate is <50%. They usually arise through the sequences of events: normal to dysplasia to carcinoma *in situ* to invasive tumours.[5,6] Previously, management of UC was based on conventional histologic parameters. However, similar UCs may show different response to treatment, which is the evidence of molecular heterogeneity among histologically similar tumours. Intensive molecular research over the last few decades have provided great insight into the biology of UC. Molecular technologies have facilitated the identification of molecular pathways and predicted outcomes of BC, thereby potentially improving life expectancy of patients.[7,8]

MOLECULAR BASIS OF CARCINOGENESIS IN ADVANCED BLADDER UROTHELIAL CARCINOMA

The molecular basis of carcinogenesis in advanced bladder UC includes: self-sufficiency in growth (epidermal growth factor receptor [EGFR] and hepatocyte growth factor); insensitivity to inhibition of growth (p *RB*, p53, and p27); evasion of apoptosis (p53, Fas, cluster of differentiation 40, and B cell lymphoma 2 [Bcl-2]); unlimited ability to replicate (telomerase increase); angiogenesis (vascular endothelial growth factor [VEGF], cyclooxygenase-2 [COX-2], platelet-derived growth factor, IL-8, and basic fibroblast growth factor); thrombospondin, angiostatin, and endostatin; tissue invasion (matrix metalloproteinase tissue inhibitor of metalloproteinase); and metastasis (P-cadherin, E-cadherin, β-catenin, and cluster of differentiation 44).

NEW ERA OF MOLECULAR MARKERS AND INVASIVE BLADDER CARCINOMA

Over the last few decades, cisplatin-based chemotherapy has been practiced as the first-line treatment in advanced UC; no potential

progress has been evident in the treatment of MIBC. As cisplatin-based chemotherapy is effective in only 30–40% cases of BC, novel therapeutic approaches are crying demand for this lethal cancer.[9]

New insights into the molecular pathology of BC have focused on some promising therapeutic targets.[10] The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, the mitogen-activated protein kinase pathway, *CDKN2A*/*CDK4*/*CCND1* and receptor tyrosine kinases/Ras pathways (including *ERBB2* [*HER2*], *ERBB3*, and *FGFR3*, as well as chromatin regulatory genes) have critical role in bladder tumourigenesis, specifically in high-grade urothelial carcinomas.[11,12] So, further exploration of this pathways in BC is important for prognostic information and targeted therapy.

In the following discussion, UC related proto-oncogenes and tumour suppressor genes and growth factors are emphasised with their therapeutic implication in invasive BC.

TUMOUR SUPPRESSOR GENES

p53

Wild-type p53 promotes anti-cancer activity by inducing cell cycle arrest, apoptosis in response to DNA damage, genomic stability, and inhibition of angiogenesis. On the other hand, the mutant p53 loses its anti-tumour effect and induces abnormal gene expression, thereby leading to tumour progression.[13,14] A Phase II clinical trial on the ubiquitin–proteosome proteolytic pathway that regulates metabolism p53 has been conducted by using proteosome inhibitor (bortezomib) in 18 patients with advanced or metastatic UC, and found no effect on its own

Gene therapy by adenoviral vectors on pre-clinical BC cell lines are also on trial to transduce cells for producing the p53 protein; and the preliminary results are promising.[15,16]

Rb

The *Rb* gene is responsible for progression of UC. The incidence of *Rb* mutations is higher in invasive UC (about 37%). There is evidence to support the association between the loss of *Rb* gene expression and progression of UC in patients with muscle invasive cancer. Pre-clinical trials on adenoviral vectors have also produced optimistic results when investigating transduction of BC cell lines with the *Rb* gene.[17,18]

PROTO-ONCOGENES

B cell lymphoma 2

Mutations of proto-oncogenes result in the over-expression of gene product or altered proteins.[19] Bcl-2 is a key protein regulator for the cell cycle and apoptotic pathway. Apoptosis is an essential mechanism for radio- and chemotherapy induced cell death. Overexpression of Bcl-2 alters the sensitivity of chemo- and radiotherapy to tumour cells.[20,21] Pollack et al.[22] analysed 107 patients where only 16 cases were upstaged and 75% (12 cases) of these tested Bcl-2 positive by immunohistochemical analysis. Yet only 24% of those that exhibited Bcl-2 overexpression were upstaged. So, they hypothesised that Bcl-2 overexpression was associated with impaired radiation response in patients with invasive BC treated with pre-operative radiotherapy.[22] In BC cell lines, antisense oligonucleotides (oblimersen) down-regulate Bcl-2 expression and enhance apoptosis in response to chemotherapy. The oblimersen Bcl-2 antisense therapy represents a promising new apoptosis-modulating strategy and pre-clinical trials support this synergistic therapeutic role for oblimersen with cytotoxic drugs.[23,24]

C-erb B-1 and *C-erb B-2*

C-erb B-1 and *C-erb B-2* oncogenes encode transmembrane proteins and EGFR and *HER2*, respectively.[25] Identification of predictive biomarkers of EGFR targeted therapy can improve the development of anti-EGFR drugs. Rebouissou et al.[26] reported EGFR as a potential therapeutic target for MIBC displaying basal-like phenotype. Another EGFR inhibitor, gefitinib had shown promising result during clinical trials in combination with gemcitabine and cisplatin.[27] Some Phase II/III trails on dual inhibitors of ErbB-1 and ErbB-2 receptor tyrosine kinases such as lapatinib were proven to be well tolerated in patients with EGFR and/or *HER2* overexpressing MIBC.[28,29]

A standardised trail on 1,005 patients with MIBC by Laé et al.[30] showed that approximately 5% of MIBC had *HER2* gene amplification. There are several ongoing clinical trials to identify potential candidates for targeted therapy in MIBC patients with *HER2* overexpression. A Phase II trial has examined the response of trastuzumab (monoclonal antibody) in 59 patients with muscle invasive *HER2* over-expressive BC and documented 73% response rate.[31] A Phase II trial of 44 cases of HER2 positive UC showed a 70% response when evaluating trastuzumab in combination with chemotherapeutic drugs such as paclitaxel, gemcitabine, and, carboplatin.[32]

PI3K/Akt/mTOR Pathway

The mTOR pathway plays a vital role in the development UC. This pathway includes upstream activators such as PI3K and Akt, negative regulators such as tuberous sclerosis 1 and 2, and downstream effectors such as p70 S6 kinase and eukaryotic initiation factor 4E. Due to its basic role in tumour growth, researchers have focused on developing targeted therapy on the mTOR.[33] Based on durable response in other tumours and pre-clinical trails in BC cell lines, buparlisib (PI3K blockade) is being investigated as a second-line treatment for patients with advanced UC.[34] Again, NVP-BEZ235 (dual PI3K/mTOR inhibitors) showed significant anti-tumour effect on cisplatin-resistant BC cells lines, but it can activate mitogen-activated protein kinase/extracellular signal-regulated kinase pathway.[35] A Phase II study on 45 patients evaluated the role of everolimus (mTOR inhibitor) in advanced UC, but effective response was documented in only three cases.[36]

ANGIOGENIC-ANTIANGIOGENIC FACTORS

Vascular Endothelial Growth Factor

VEGF proteins and gene expressions are detected at high levels in high-grade and muscle invasive UCs and are associated with poor survival.[37,38] Again, some studies showed that VEGF expression was significantly higher in non-MIBC compared to MIBC as the rate of tumour growth is higher at the early stage of the disease.[39,40] So, the inhibition of VEGF transcripts significantly reduces the proliferation rate of the bladder cancer cells[41] and blockade of VEGF receptor reduces growth and invasion of bladder cancer cells.[42,43] Bevacizumab (VEGF antibody) and ramucirumab (VEGFR2 antibody), used in combination with chemotherapy, showed promising result in Phase II clinical studies of advanced UC. There are multiple ongoing Phase II trials with other agents targeting VEGF receptors, including sunitinib, sorafenib, and pazopanib.[44,45]

Cyclooxygenase-2

The selective COX-2 inhibitor celecoxib has chemo-protective activity against various cancers, including BC. It inhibits the proliferation, migration, invasion, and epithelial-to-mesenchymal transition of BC cells.[46] Epidemiological and pre-clinical evidence suggest that COX-2 inhibitors are promising target for BC. COX-2 expression in the UC is associated with a high grade and an advanced stage, and is an independent predictor of disease progression and survival. However, future trials on COX-2 inhibitors should be tested as a standardised therapy to improve the effectiveness of drugs.[47]

Thrombospondin-1

Down-regulation of thrombospondin-1 (TSP-1) expression is independently associated with cancer recurrence and mortality. Loss of TSP-1 expression is associated with alterations in other cell cycle regulators such as p21, p53, and p27 expression.[48] The newer molecular agents such as the TSP analogue (ABT-510) and TSP-1 mimetics (D-isoleucyl enantiomer TSP-1 heptapeptide) are in Phase II clinical trials, which have been shown to reduce micro-vessel density and increase apoptosis in bladder tumours.[49,50]

The genes, proteins, and molecules with the potential to alter the muscle invasive UCs with their therapeutic targets are shown in Table 1.

Some key messages should be pointed out. For instance, many predictive biomarkers were investigated (e.g., serum VEGF, circulating tumour cells, and defects in DNA damage repair genes, which involve *ERCC2*, *ATM*, *RB1*, and *FANCC*). These biomarkers can predict responses to cisplatin-based neoadjuvant chemotherapy in many patients with MIBC.

Table 1: Summary of genes and molecules with potential therapeutic targets.

Genes and molecules	Potential therapeutic targets
p53	Bortezomib (proteosome inhibitor); gene therapy by adenoviral vectors
Rb	Gene therapy by adenoviral vectors
Bcl-2	Oblimersen (antisense oligonucleotides)
C-erb B-1 *C-erb B-2*	Gefitinib; lapatinib Trastuzumab (monoclonal antibody)
PI3K	Buparlisib (PI3K blockade); NVP-BEZ235 (dual PI3K/mTOR inhibitors)
mTOR	NVP-BEZ235 (dual PI3K/mTOR inhibitors), everolimus (mTOR inhibitor)
VEGF	Bevacizumab (VEGF antibody); ramucirumab (VEGFR2 antibody); sunitinib, sorafenib, and pazopanib (VEGF receptors)
COX-2	Celecoxib (COX-2 inhibitor)
TSP-1	ABT-510 (TSP analogue); D-isoleucyl enantiomer (TSP-1 hep-tapeptide and TSP-1 mimetics)

Bcl-2: B cell lymphoma 2; COX-2: cyclooxygenase-2; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase; TSP-1: thrombospondin-1; VEGF: vascular endothelial growth factor.

In addition, high tumour mutational burden has been associated with response to immune checkpoint inhibitors in metastatic BC. Studies evaluating immune checkpoint inhibitors in the neoadjuvant setting, using pembrolizumab or atezolizumab before radical cystectomy in patients with MIBC (e.g., PURE-01 study and ABACUS study)[51] have shown some conflicting results, and, thus, more research is needed. Moreover, programmed death-ligand 1 expression by immunohistochemistry and high tumour mutational burden has demonstrated predictive value in some MIBC settings, but additional studies are merited to explore this topic.

Overall, prognostic and predictive molecular biomarkers will present important adjuncts to current clinical and pathological data. However, large-scale Phase III randomised clinical trials with long-term follow-up are necessary to further investigate this area.

CONCLUSION

Urologists are still treating BC depending on disease stage. Resection of tumour, intravesical mitomycin C, and Bacillus Calmette–Guérin immunotherapy, followed by surveillance are treatment of choice for non-MIBCs. Muscle invasive carcinomas (stage T2) are treated with either radical cystectomy followed by radiotherapy, while metastatic diseases are treated by adjuvant or neoadjuvant chemotherapy. These treatment protocols have improved the disease-free survival; however, overall survival has remained unchanged. Therefore, establishing new treatment regimens for MIBC for better management and overall survival is a crying need. Recent and on-going randomised control trials on molecular biomarkers in muscle invasive disease will be needed to evaluate the precise role and ideal regimen for MIBC.

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Paraneoplastic Hypercalcaemia as a Cause of Unexplained Renal Impairment in a Patient With Seminoma: A Case Report

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Abstract

A 44-year-old otherwise healthy male who had undergone left high inguinal orchidectomy, with histopathology suggestive of classical seminoma, was referred to the authors' oncology centre for evaluation of persistently deranged renal function tests and initiation of chemotherapy. They had a large retroperitoneal mass encasing their left kidney and their creatinine was 4.2 mg/dL. Even 1 week after double J stenting, they had persistently elevated creatinine of 3.1 mg/dL, which was precluding their curative chemotherapy with bleomycin/cisplatin/etoposide regimen. In a desperate situation, to prevent further progression of disease, pre-phase chemotherapy with carboplatin and etoposide was considered. In anticipation of tumour lysis syndrome, considering the large mass and compromised renal function, a tumour lysis profile was requested, which revealed elevated serum calcium levels (15.4 mg/dL, which goes against the tumour lysis syndrome). Considering the large retroperitoneal lymph nodal mass, suppressed parathyroid hormone levels (4.1 pg/mL) and vitamin D3 being within normal range, a paraneoplastic cause of hypercalcaemia was considered. Correction of hypercalcaemia with medical measures as well as treatment of seminoma was instituted, which led to normalisation of renal function tests within the next 10 days. Here, the authors report a rare case of testicular seminoma with persistently deranged renal function, likely due to paraneoplastic hypercalcaemia, which improved after successful chemotherapy along with anti-hypercalcaemic measures, including aggressive hydration, diuretics, calcitonin, dexamethasone, and denosumab. This report shows that it is important to treat the cause along with medical management in this oncologic metabolic emergency. It also highlights the value of pre-phase chemotherapy with carboplatin and etoposide in the setting of acute renal impairment.

Key Points

1. Paraneoplastic hypercalcaemia leading to impaired renal function can rarely occur with seminoma presenting as a large retroperitoneal mass.

2. Although obstructive uropathy is a common and logical consequence of a large retroperitoneal mass accompanied by renal impairment, medical causes must be considered if successful stenting of ureters does not improve renal function.

3. Treatment of the hypercalcaemia and the seminoma with non-nephrotoxic chemotherapy such as carboplatin and etoposide leads to rapid resolution of both the renal impairment and the tumour.

BACKGROUND

Testicular seminomas are the most common type of testicular germ cell tumours.[1] It typically affects young males between the ages of 30–55 years. Because of its high sensitivity to chemotherapy and radiotherapy, these tumours have high cure rates.[2] Neoplasm is the most common cause of hypercalcaemia in hospitalised patients. Paraneoplastic hypercalcaemia affects about 20% of all patients with cancer.[3] However, its incidence is very rare in testicular seminomas, with only few cases reported in the last five decades.[4-9] Here, the authors report a case of seminoma complicated by paraneoplastic hypercalcaemia. This case report signifies the importance of treating the principal cause of hypercalcaemia along with the value of pre-phase chemotherapy with carboplatin and etoposide in germ cell tumours.

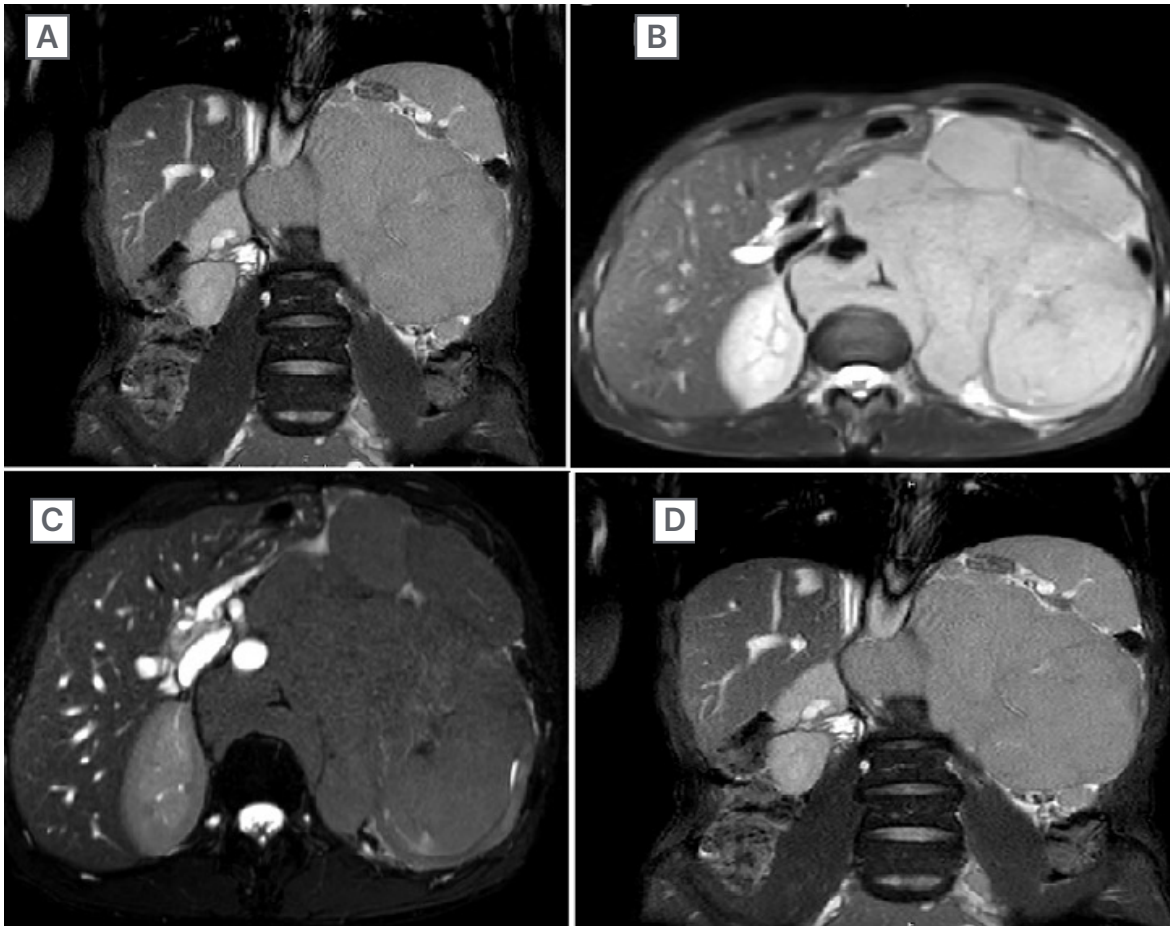
CASE PRESENTATION

A 44-year-old male was referred to the authors' oncology setup for evaluation of deranged renal function tests (RFT) and for initiation of chemotherapy. One month prior to admission, they presented to their local hospital with history of abdominal pain, left testicular swelling, loss of appetite, and significant weight loss of 3 months duration. Ultrasonography of the abdomen and pelvis showed a large mass in the region of the left kidney, which was not seen as a separate structure. Sonography of the inguinoscrotal region showed enlarged (7.7×4.2×5.0 cm), lobulated left testis with altered echotexture suggestive of a testicular tumour. Their creatinine at this point of time was 3.39 mg/dL. In view of raised creatinine, a plain CT study of the abdomen and pelvis was done, which showed enlarged left kidney and a large retroperitoneal mass lesion measuring 15×14×12 cm, suggestive of lymph nodal metastasis. They previously underwent left high inguinal orchidectomy at a different hospital, which on histopathology was suggestive of classical seminoma.

Their chest X-ray was normal, their β-human chorionic gonadotropin was moderately raised (898.7 IU/L), and their α-fetoprotein was normal. Therefore, they were categorised as good risk seminoma according to the International Germ Cell Consensus Classification. The standard of care in good risk seminoma is chemotherapy with three cycles of bleomycin/cisplatin/etoposide (BEP) regimen. However, 3 weeks post-high inguinal orchidectomy, their serum creatinine remained elevated at 4.2 mg/dL, their blood urea nitrogen was 98.4 mg/dL, and this was deterring their further treatment with chemotherapy. The MRI study of abdomen and pelvis showed multiple enlarged discrete as well as conglomerate lymph nodal mass lesions involving retroperitoneum and left renal pelvis/renal fossa, with extensions across midline to right side threatening to encase the right ureter (Figure 1). Therefore, they underwent a cystoscopy and right double J (DJ)-stenting as a preventive measure.

With aggressive hydration, the serum creatinine improved to 2.9 mg/dL and blood urea nitrogen to 86.4 mg/dL. One week post-DJ stenting, they presented with complaints of back pain and loss of appetite. At this time, their serum creatinine was persistently elevated at 3.05 mg/dL, blood urea nitrogen at 106.10 mg/dL, lactate

Figure 1: Image showing the retroperitoneal mass with extents.



A large retroperitoneal metastatic mass occupying and engulfing the kidney (A) and also crossing over to the right side (B). The mass has also engulfed and displaced the aorta with angle of contact >180° (C). The contrast-enhanced images in (C) and (D) show function loss of the left kidney.

dehydrogenase at 593.00 U/L, and phosphorous at 5.70 mg/dL. They were referred to medical oncology for management of retroperitoneal mass with elevated lactate dehydrogenase and β-human chorionic gonadotropin in the context of a deranged RFT. The standard BEP regimen could not be initiated in the authors' patient due to impaired renal function.

In anticipation of tumour lysis syndrome due to compromised renal function, a tumour lysis profile was done 7 weeks from diagnosis, which revealed an elevated calcium level at 15.4 mg/dL (corrected calcium level; calcium: 15mg/dL; albumin: 3.4mg/dL). Considering the clinical context, a paraneoplastic cause of elevated calcium was suspected, which was corroborated by parathyroid hormone (PTH) levels that were suppressed at 4.1 pg/mL (normal: 10.0-55.0 pg/mL) and vitamin D3 levels that were within normal range. A PTH-related peptide (PTHrP) assay was not done, as this investigation was not available at the authors' hospital. The patient was initiated on antihypercalcaemic measures (aggressive hydration, calcitonin, furosemide, and denosumab), as well as pre-phase chemotherapy with carboplatin (a one-time 150 mg flat dose) and etoposide (100 mg flat dose for 3 days; etoposide requires 25% dose reduction if creatinine clearance is 15–50 mL/min; therefore, its adjusted renal dose is approximately 100 mg).

Their creatinine levels began to decline mirroring the fall in serum calcium (Figure 2). Their creatinine clearance (estimated by the Cockcroft-Gault method) improved from 12.95

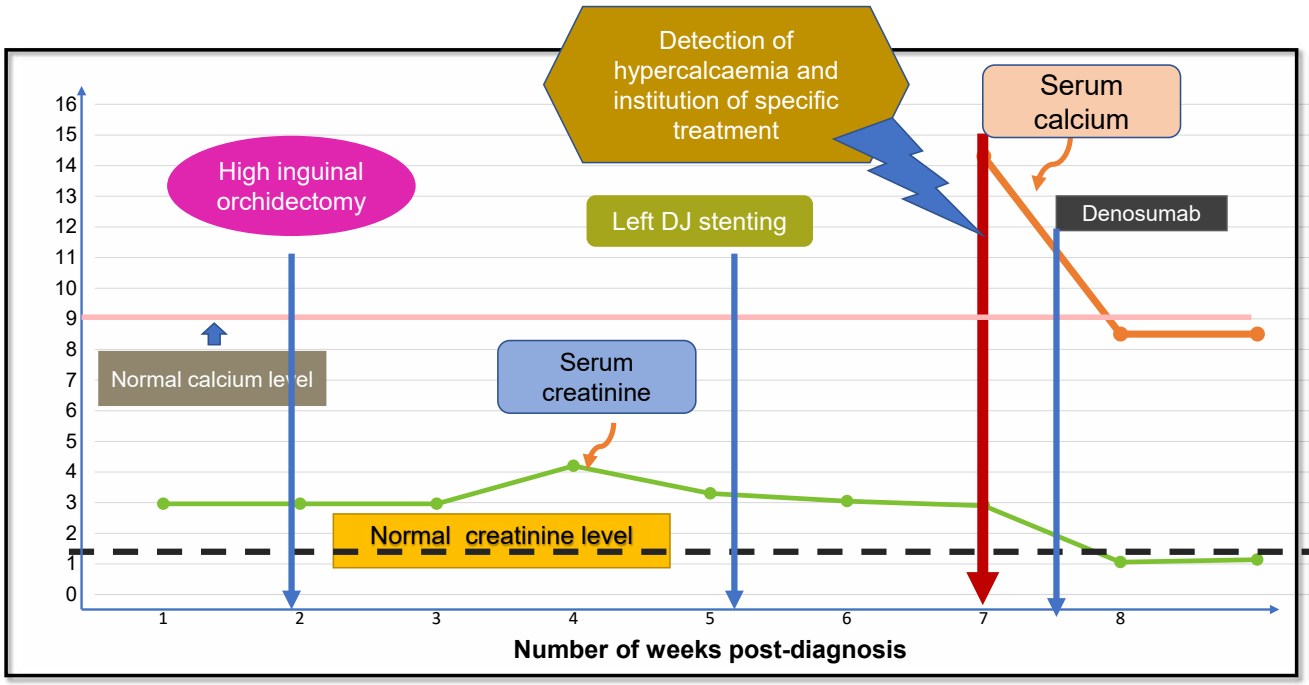
mL/min to 56.60 mL/min. Corresponding to the decrease in corrected calcium and creatinine levels, an ultrasonography of abdomen and pelvis 6 days after the initiation of chemotherapy showed regression of mass from 17×13×12 cm to 17×7×11 cm. At discharge, their serum creatinine had come down to 1.04 mg/dL, urea to 44.3 mg/dL, phosphorous to 1.8 mg/dL and calcium to 8.5 mg/dL. They were subsequently planned for the standard three cycles of BEP as recommended for good risk seminoma. The DJ stent removal was done 3 days after their renal parameters stabilised. Their appetite improved as well, and their weight increased from 40 to 45 kg. A timeline chart representing the major events in this case is represented in Figure 2.

DISCUSSION

This case report is to highlight a rare metabolic cause of renal impairment due to hypercalcaemia in a patient with a testicular tumour and a large retroperitoneal mass. In the clinical situation of large retroperitoneal mass and deranged RFTs, the usual suspicion is of obstructive uropathy. Therefore, a right DJ stent was prophylactically placed to preserve right kidney function and prevent further renal impairment. However, these measures did not improve the renal functions and the raised creatinine levels remained an unsolved problem in this patient. They were incidentally detected to have hypercalcaemia on a tumour lysis profile, which is a feature against the occurrence of tumour lysis syndrome. In individuals with paraneoplastic hypercalcaemia, a low-to-normal PTH level, typically high PTHrP levels, along with elevated calcium levels, are the common laboratory findings.[10] Although PTHrP levels were not determined in the authors' patient, low PTH with normal vitamin D and elevated calcium levels indicated hypercalcaemia of malignancy, possibly due to secretion of PTHrP by tumour cells.

Since the likely cause of hypercalcaemia was malignancy, its correction would not occur until the underlying cause, which is seminoma, would be treated. They were, therefore, started on carboplatin and etoposide without delay, along with anti-hypercalcaemic measures. This report also highlights the value of 'pre-

Figure 2: Timeline of events from diagnosis.



DJ: double J.

phase' chemotherapy with carboplatin, which is considered an inferior drug compared to cisplatin in the chemotherapy of germ cell tumours. In a hypercalcaemic state, renal insufficiency can be caused by pre-renal involvement, direct modifications in intravascular tone, and glomerular permeability. According to a study, renal function improved in all instances when serum calcium levels dropped with the treatment of hypercalcaemia.[11] The approach to hypercalcaemia management depends on the severity of hypercalcaemia. Patients with severe hypercalcaemia are primarily managed with intravenous hydration, along with calcitonin to prevent calcium resorption from the bone.[3]

In the authors' patient, furosemide was used to increase urine output, prevent fluid overload, and enhance calcium excretion. Bisphosphonates such as zoledronic acid are the treatment of choice for treating paraneoplastic hypercalcaemia. Since it takes 2–3 days to begin its action, its use is not ideal in an emergency,[12] and since nephrotoxicity hinders its use in renal failure,[3] it was avoided in the authors' patient. Unlike bisphosphonates, calcitonin exhibits quick onset of action and is, therefore, utilised for an emergency.[13] However, its clinical value is limited because of downregulation of calcitonin receptors resulting in tachyphylaxis within 48 hours of its initiation. The addition of glucocorticoids leads to upregulation of calcitonin receptor and boost the impact of calcitonin.[14,15] To aid patients who have failed to respond to bisphosphonates or who are unable to take bisphosphonates due to severe renal impairment, denosumab is the new option.[16]

CONCLUSION

In summary, paraneoplastic hypercalcaemia is a rare scenario in classical seminoma. Pre-phase chemotherapy with carboplatin and etoposide to treat the underlying cause of hypercalcaemia concurrently with aggressive hydration, calcitonin, bisphosphonates/denosumab, diuretics, and dexamethasone aided in resolving hypercalcaemia, as well as restoration of normal renal function in the authors' patient. This case report signifies the importance of treating the principal cause of hypercalcaemia along with the value of pre-phase chemotherapy in the setting of acute renal impairment.

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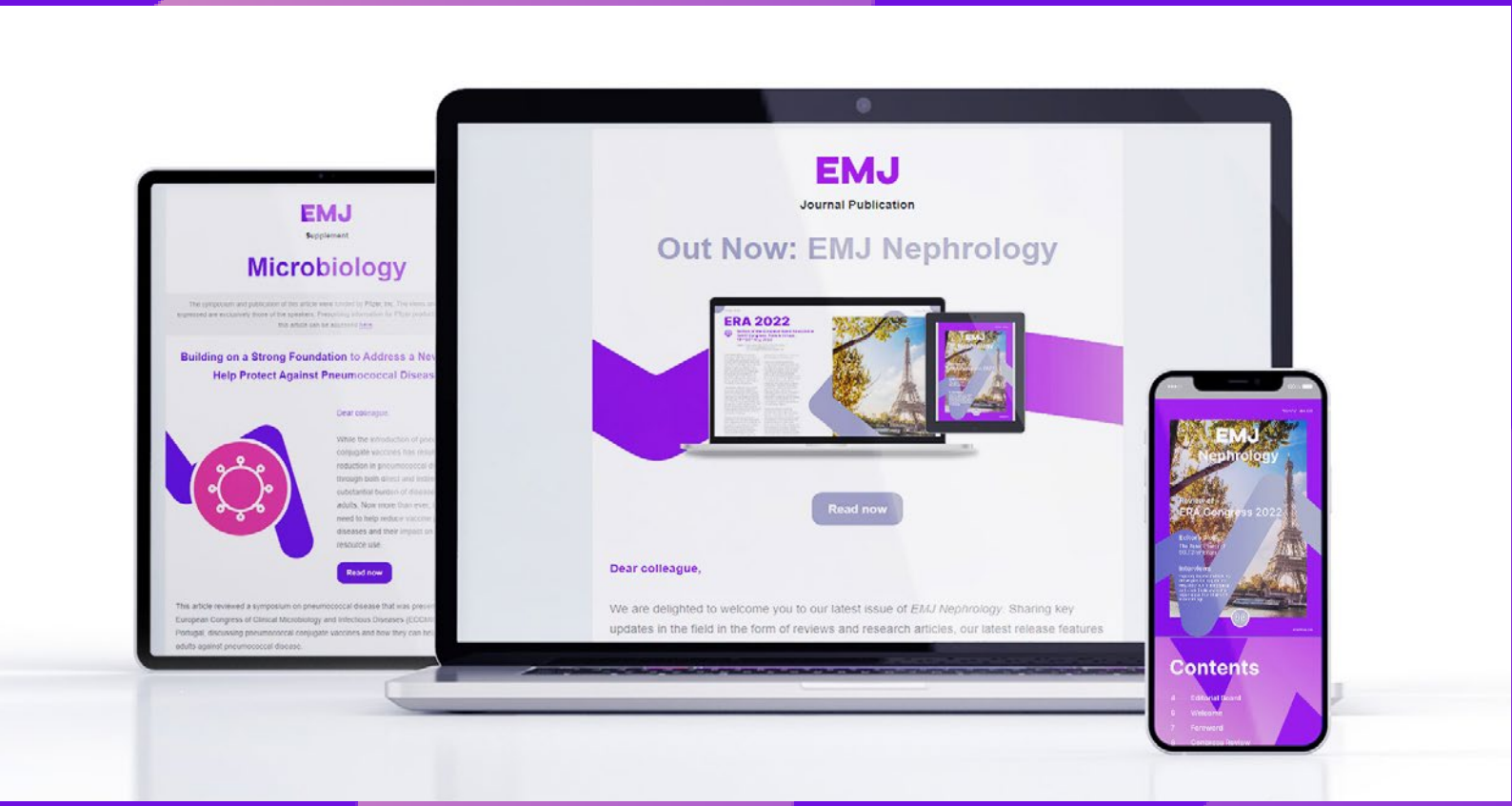

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