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UROLOGY

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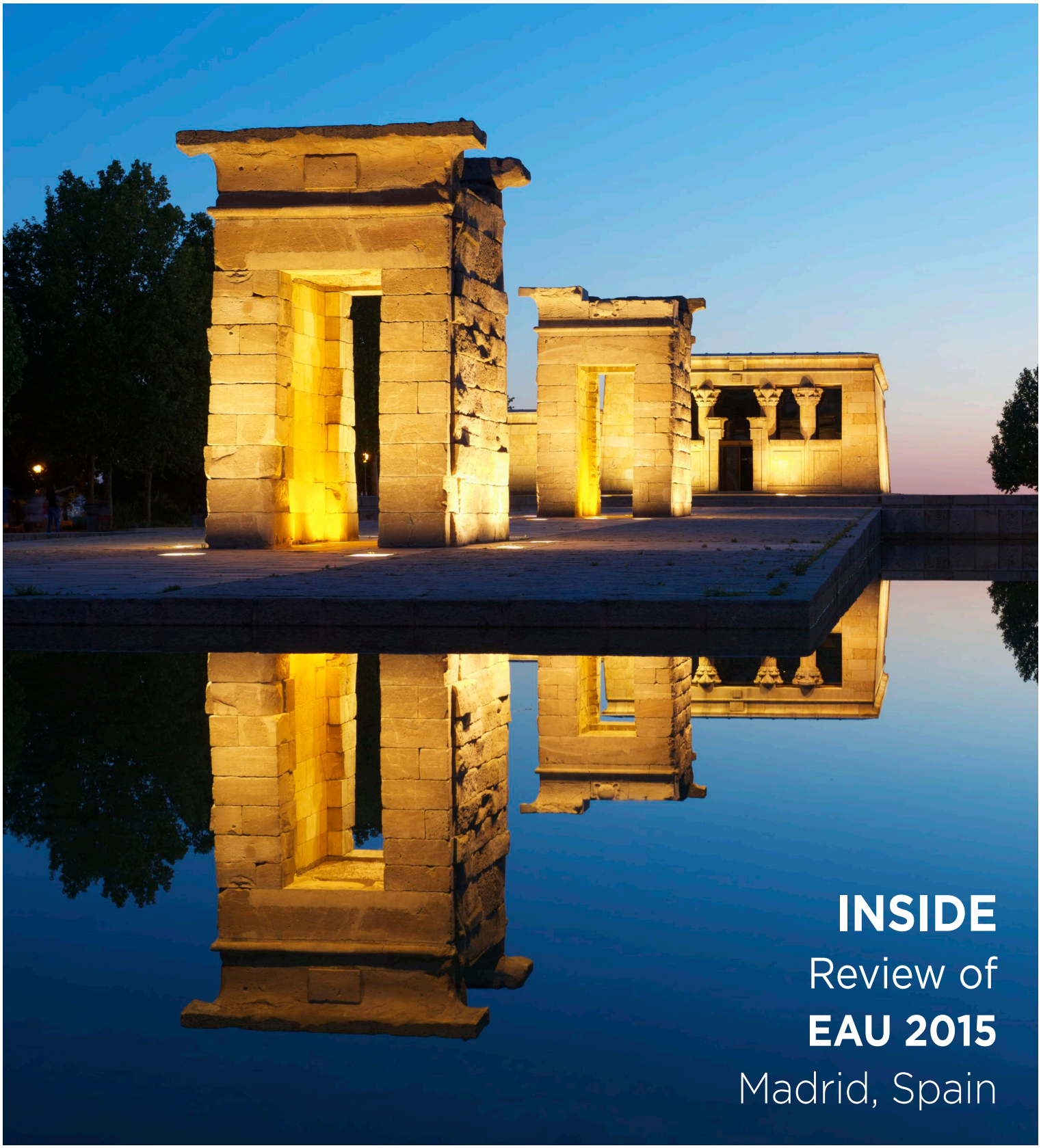

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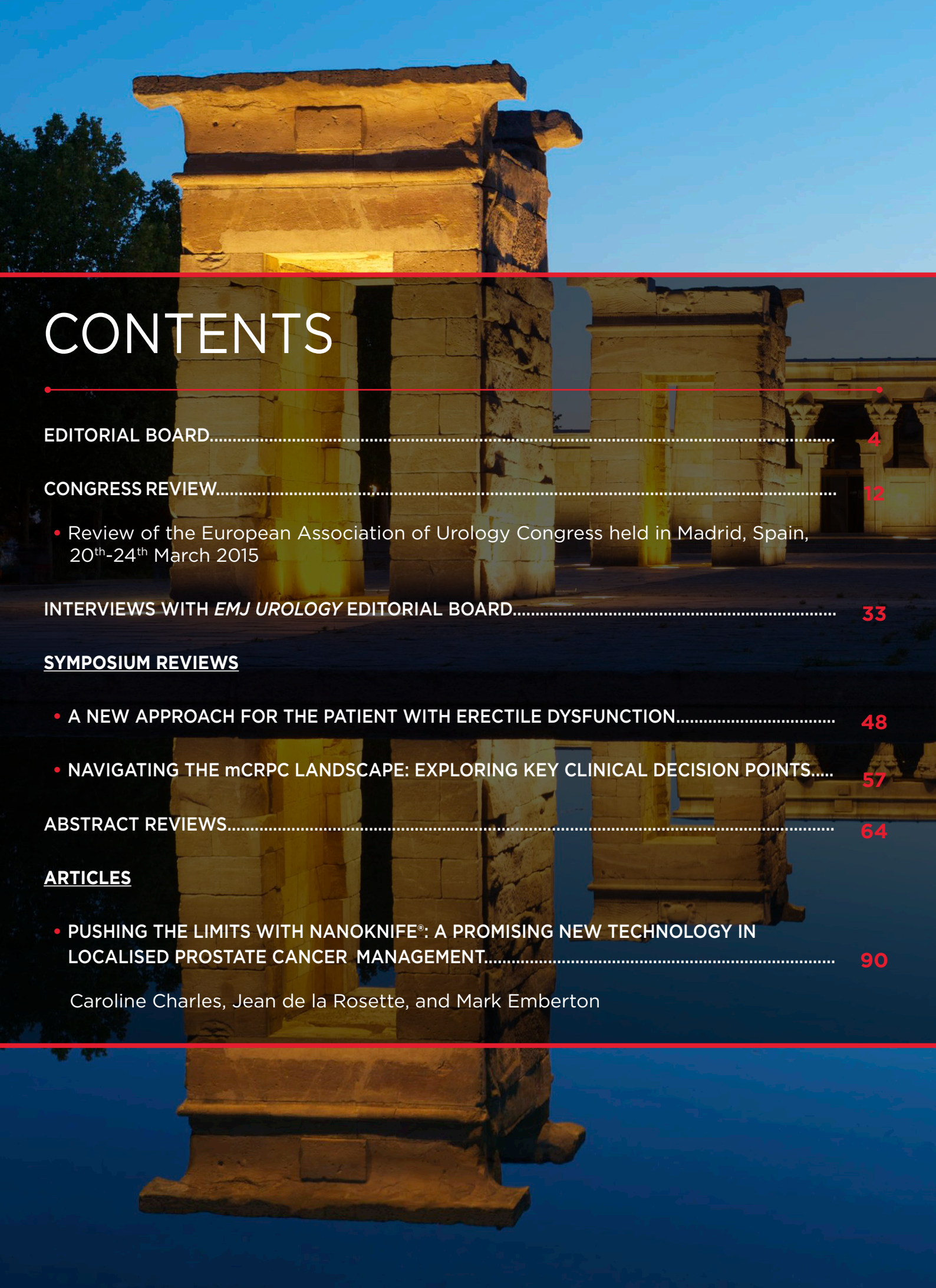
EAU 2015

Madrid, Spain



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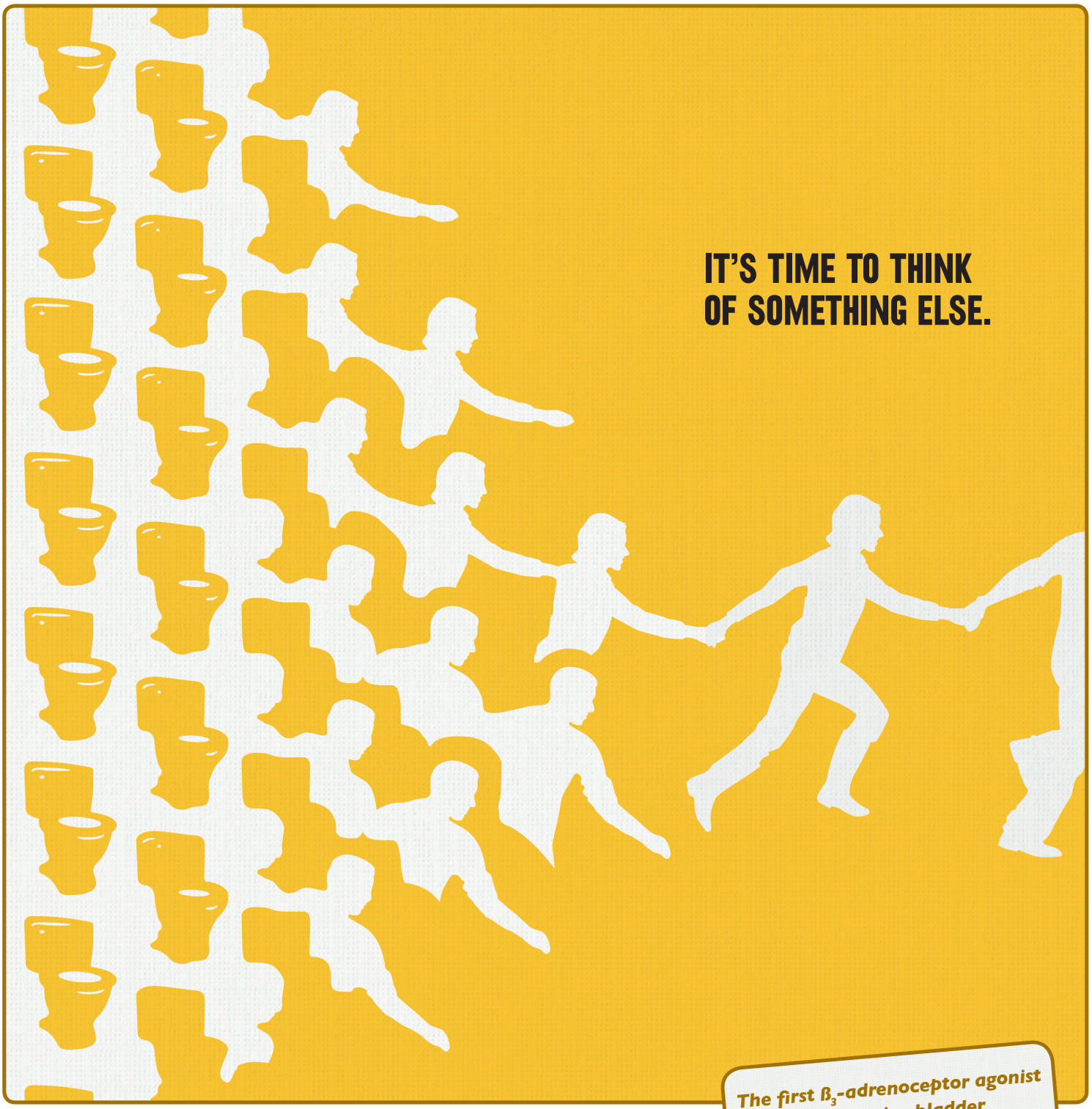
Urology



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EMJ GORELY NEW MEDIA

European Medical Journal
EMJ Urology Vol 3.2
May 2015

The MedBIC,
Anglia Ruskin University,
Chelmsford, CM1 1SQ

Welcome

Hello and welcome to the second edition of *European Medical Journal Urology,* our publication devoted to covering recent developments in all of the sub-disciplines in this diverse field of medicine. We have dedicated this edition of *EMJ Urology* to reporting the latest data and talking points raised at the recent annual congress of the European Association of Urology (EAU) – Europe's largest urological meeting. Mirroring the diversity of the content presented at EAU 2015, this edition of our journal features an in-depth review of the topics presented, interviews with those presenting, peer-reviewed articles written by prominent urologists, and a summary of other news that emerged during the meeting.

Given its position as the most common cancer in European men and the third-most common overall, much of the scientific programme was dedicated to the diagnosis and management of prostate cancer. In this edition of *EMJ Urology,* Prof Jean de la Rosette and Prof Mark Emberton explore with Dr Caroline Charles the promising perspectives offered by irreversible electroporation, a novel minimally invasive treatment option for prostate cancer patients.

Benign prostatic hyperplasia (BPH) also remains a common condition in older men, and the ageing populations present in many European countries mean that effective (and cost-effective) treatment options are required by patients, physicians, and healthcare providers alike. Inside this issue we have included peer-reviewed articles on the treatment of BPH. Dr Marc Fourmarier reports on his institute's experience with the use of holmium laser enucleation of the prostate (HoLEP) for the treatment of day-case patients, and highlights the promising results obtained in terms of patient satisfaction and morbidity, although the need for excellent organisation within the whole care-delivery team is paramount. Staying with the topic of HoLEP, Dr Cesare Marco Scoffone and Dr Cecilia Maria Cracco describe their experience using and adapting the technique over a period of 4 years in the treatment of more than 200 cases. As well as HoLEP, another alternative to transurethral resection of the prostate is the use of the Greenlight XPS laser system for photovaporisation of the prostate gland, and in this issue Prof Andrea Tubaro and Dr Cosimo De Nunzio describe how this technique may provide an alternative treatment option for high-risk patients on anticoagulants or antiplatelet therapy.

With so much new scientific content to take in, we hope you enjoy reading our latest edition of *EMJ Urology* and that you are already beginning to look forward to EAU16, which is to be held in Munich, Germany next year – we look forward to seeing you there!

Spencer Gore

Team Principal, European Medical Journal

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Foreword

Dr A. Erdem Canda

Associate Professor of Urology,
Yildirim Beyazit University, Ankara, Turkey

Dear Colleagues,

It is a great pleasure to introduce you to the May 2015 issue of *European Medical Journal Urology.*

The main highlight of this edition is the comprehensive coverage of the 30th Anniversary European Association of Urology 2015 (EAU15) Congress, held on 20th-24th March 2015 in Madrid, Spain under the theme of 'Sharing Knowledge - Raising the Level of Urological Care', which proved to be another great success for the EAU. This meeting is Europe's biggest urological meeting and featured 5 days of lectures, debates, European School of Urology (ESU) courses, and approximately 1,200 poster, oral, and video abstract presentations. EAU15 attracted more than 10,000 delegates from 120 countries, boasted an exhibition of over 100 companies, and incorporated section meetings and live surgery in 23 simultaneous session rooms. Innovative surgical procedures, performed at university hospitals, were also broadcast during the congress.

> "This meeting is Europe's biggest urological meeting and featured 5 days of lectures, debates, European School of Urology (ESU) courses, and approximately 1,200 poster, oral, and video abstract presentations."

Forming part of a stellar line-up of activities and sessions was 'Urology Beyond Europe', a day-long programme that allowed leading international urologists to discuss the enormous and rapid regional advances made in urology worldwide. A range of plenary, thematic, and abstract sessions covered state-of-the-art treatment strategies and prominent research updates. The sparkling scientific programme proved an eye-opening feast, giving all who attended extra fuel for future clinical research and providing the platform for an enthralling series of lectures and debates.

Additionally, the 11th Turkish National Endourology Congress, held on 23rd-26th April 2015 in Antalya, Turkey, will be featured in EMJ's next congress review publication. This congress was a great success with strong international participation, and all sessions were translated into English. Laparoscopy, percutaneous nephrolithotomy, and retrograde intrarenal surgery courses were organised and attracted great interest.

I hope that you enjoy reading the new issue!

Yours sincerely,

A. Erdem Canda

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

EAU ANNUAL CONGRESS 2015

IFEMA - FERIA DE MADRID, MADRID, SPAIN

20TH - 24TH MARCH

Welcome to the *European Medical Journal* review of the European Association of Urology Congress 2015

On 20th-24th March 2015 The European Association of Urology (EAU) hosted Europe's largest scientific meeting dedicated to this rapidly evolving field of medicine in Madrid, Spain. Madrid's beautiful blend of historic and modern architecture provided the perfect backdrop for this auspicious meeting. Attracting more than 12,000 participants representing 117 countries, and with over 4,000 scientific contributions up for discussion, this 30th anniversary of EAU's Annual Congress was truly a memorable event.

The congress started in a celebratory mood as the Chattanooga Big Band played upbeat live music to welcome the delegates, who were also given a taste of traditional Spanish music and dance in the form of an energetic live flamenco performance from the Ballet Carmen Cantero. When the opening introductions were complete, a wide range of awards were presented to honour the achievements of outstanding dignitaries, in recognition of their extraordinary scientific accomplishments in the field of urology. The honoured individuals have shown eminence, commitment, devotion, and fortitude through the advancement of the discipline, potentially impacting the way in which urological conditions are diagnosed and treated.

"When I took this position in 2007, it was my ambition to see the association better off when I leave. Looking at all of our achievements set out during this General Assembly, we can conclude this is the case."

The main awards given were the Willy Gregoir Medal, which was presented to Prof Laurent Boccon-Gibod (France) for significant contribution to the development of the urological specialty in Europe; Prof Humberto Villavicencio (Spain) was the recipient of the Frans Debruyne Life Time Achievement Award for a longstanding and important contribution to the activities and development of the EAU; the 18th Crystal Matula Award was presented to Dr Morgan Rouprêt (France), an esteemed award for a promising young European urologist; Prof Stavros Tyritzis (Greece) received the Hans Marberger Award for the best European paper published on minimally invasive surgery in urology. Additionally, Professors Gopal Badlani (USA), Keong Tatt Foo (Singapore), and Ladislav Jarolim (Czech Republic) were appointed as the new EAU honorary members.

The presentation and event formats were used to communicate new findings from clinical and pre-clinical research, the variety of which helped keep delegates focused and playing an active role in the meeting's debates. The congress included traditional lectures and poster sessions, as well as plenary sessions, live surgery demonstrations, hands-on training courses, technical exhibitions from industrial manufacturers, and a historical exhibition showcasing how urology has developed over the years. New innovations introduced at this year's congress included the use of multimedia ePosters designed to help translate the science in a more engaging way, as well as a new badge-tracking system designed to make it as easy as possible for delegates to network with one another.

Similarly to last year's meeting, the screening, diagnosis, and clinical management of prostate cancer was the most prominent topic covered in the various sessions and was the subject of considerable debate. Other key topics that received significant coverage during the congress included: appropriate management of bladder and kidney tumours, urological aspects of nephrectomy and renal transplantation, incontinence, and sexual dysfunction.

The novel technical innovations at the conference were not the only change at EAU15 as the event marked the final congress headed by outgoing EAU Secretary General Prof Per-Anders Abrahamsson. Prof Abrahamsson handed over to Prof Chris Chapple, who had been acting as Secretary General-Elect for the previous 12 months. In his congress-opening speech, Prof Abrahamsson summarised his experience with the EAU: "I have served this wonderful organisation for 11 years and it has been the best journey of my life." Prof Abrahamsson was proud of the achievements of the EAU during his tenure, stating during his handover: "When I took this position in 2007, it was my ambition to see the association better off when I leave. Looking at all of our achievements set out during this General Assembly, we can conclude this is the case."

HIGHLIGHTS

Combining MRI with Conventional Prostate Surveillance May Produce a More Effective Prostate Screening System

INITIAL results from the Göteborg randomised screening trial have indicated that using magnetic resonance imaging (MRI) alongside conventional prostate cancer (PrC) screening could improve cancer detection and help avoid unnecessary biopsies. PrC is now known to be the third-most common male cancer in Europe, but prior to this there was little evidence that existing screening procedures were effective.

The Göteborg trial is one branch of the European Randomized Study of Screening for Prostate Cancer (ERSPC) – the largest trial of its kind in the world. The study's new findings were presented at EAU15, with researcher Dr Anna Grenabo-Bergdahl, Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, Göteborg, Sweden, concluding:

"From these initial results it looks like we can combine PSA [prostate specific antigen] levels with MRI scans to give more accurate screening results. This strategy would allow us to take men with lower PSA scores, and give them MRI scans, to confirm whether or not a biopsy is absolutely necessary. Another benefit is that the MRI helps us locate the suspect area, meaning that if we have to do a confirmatory biopsy, we have a much better idea of where the problem might be. This avoids patient stress, and means we are less likely to miss cancers."

Of the 384 patients who participated in the Göteborg trial, 124 patients were given an MRI scan prior to having a biopsy. Those with a suspicious MRI or with a PSA ≥3 ng/ml were referred for biopsy. The results showed that combining PSA with MRI, followed by MRI-targeted biopsy only in men with suspicious MRI, resulted in improved PrC detection compared with PSA scores alone followed by standard random biopsy. The results also proved that more significant cancers were detected with the combination

"Another benefit is that the MRI helps us locate the suspect area, meaning that if we have to do a confirmatory biopsy, we have a much better idea of where the problem might be."

of PSA and MRI compared with using PSA as a stand-alone screening test.

Dr Grenabo-Bergdahl added: "These results from the pilot study are very encouraging, but now they need to be confirmed. We are starting a trial of 40,000 patients in the Göteborg area. If we can replicate the results from our pilot study this may lead to a paradigm shift in future screening and fundamentally change the way we handle early detection of PrC."

Arv7 Takes the Lead in the mCRPC Predictive Biomarker Race

EXPRESSION of the AR-isoform encoded by splice variant 7 (ARv7), which lacks the ligand-binding domain, has emerged as the most encouraging biomarker for metastatic castration-resistant prostate cancer (mCRPC). This news was the subject of much discussion at EAU15, and was presented by Dr Robert J. van Soest, Department of Urology, Erasmus University Medical Center and Cancer Institute, Rotterdam, the Netherlands.

"Although these findings require large-scale validation, it is a promising first step towards a more personalised treatment approach in mCRPC, where ARv7 expression in circulating tumour cells might be used to facilitate treatment decisions."

Stressing the increased challenges of treatment selection that physicians and mCRPC patients face today, Dr Soest highlighted the need for predictive biomarkers to guide clinical application and trial design. With trials testing the facilitating effect of established predictive biomarkers on treatment decisions remaining scarce, biomarker-driven studies are particularly important for present mCRPC research in order to recognise mechanisms of resistance to new drugs.

ARv7 expression increases during the course of mCRPC development, and is inclined to occur in patients with more advanced disease and after previous treatment with abiraterone or enzalutamide. Men expressing ARv7 in circulating tumour cells have been shown to not respond to either abiraterone or enzalutamide treatment; clinical progression-free survival and overall survival (OS) were lower in men expressing ARv7. "Although these findings require large-scale validation, it is a promising first step towards a more personalised treatment approach in mCRPC, where ARv7 expression in circulating tumour cells might be used to facilitate treatment decisions," said Dr Soest.

Research suggests that a high Gleason score (GS) at first diagnosis serves as an independent risk factor for poor response to abiraterone as well as being indicative of patients who are likely to derive greatest OS benefit from docetaxel chemotherapy, which suggests a

potential predictive role for this clinical score. However, the COU-AA-302 trial demonstrated that, despite the OS benefit being less pronounced in patients with a high GS, there was still a clinical benefit in terms of progression-free survival (PFS) in patients receiving pre-chemotherapy abiraterone; similar results were obtained using cabazitaxel.

"Thus, GS could be useful in identifying patients who derive the most benefit from docetaxel chemotherapy, but might be of less value to predict benefit from other treatments," said Dr Soest.

Another emerging biomarker is the neutrophil to lymphocyte ratio (NLR). An elevated NLR has been found to be an independent marker of adverse results for various solid tumours including mCRPC; NLR ≥5 was associated with lower prostate-specific antigen response rates and shorter survival. Therefore, NLR represents a clinical parameter that is readily available and may have potential to guide future treatments.

Novel Sequencing Methods Reveal the Impact of STIs on Male Genital Disorders

STRATEGIC brainstorming for the prevention of prostate carcinogenesis has received a boost from a succession of findings that indicate viral infection as a major risk factor for prostate-related conditions.

For a long time the risk factors for onset of prostate cancer (PrC) have been shrouded in mystery, despite the cancer's devastating effect on the global male population. However, research has focussed on events that may influence advancement of PrC, namely histories of chronic inflammation of the prostate gland and sexually transmitted infections (STIs).

Established as a crucial and fresh approach in the discovery of new viruses in humans, metagenomics sequencing (MGS) permits

comprehensive high-throughput analyses in a sample without precursory cloning. It is very difficult to find a correlation between the presence of viral DNA and PrC onset, as DNA viruses can merge into the host genome and trigger carcinogenesis via insertional mutagenesis. "Thus, by the time PrC has been developed, no viruses could be detected with currently used 'classical' diagnostic technologies. Contrary to this, MGS allows detecting the 'signature' or 'fingerprint' of viruses or bacteria in the host cells by the time the malignancy has been developed but the causative infection has resolved," said Dr Vitaly Smelov, IARC WHO, Infections and Cancer Biology Group, Lyon, France, who presented the findings at the EAU15 conference.

A total of 27,105 subjects with prostatic chronic inflammation (no PrC arm) and 14,156 subjects with prostatic malignancy (PrC+ arm) enrolled in a recent first-in-principle study on MGS of expressed prostate secretion. Bacterial reads were recorded in 9.0% and 5.2%, while viruses were found in 6.8% and 19.9% of the no PCR and PrC+ arms, respectively, thus highlighting the possible role of viral infections in prostate carcinogenesis.

"MGS allows detecting the 'signature' or 'fingerprint' of viruses or bacteria in the host cells by the time the malignancy has been developed but the causative infection has resolved."

The evolution of our knowledge of the microbiome of the male urogenital tract may be enhanced by the analysis of prostate gland specimens taken from various male populations, through the extended use of new technologies such as MGS. Identifying viral infections in the pre-cancer period is greatly encouraged in order to minimise the chance of misleading data through the use of current classical technologies, while evaluating the influence of more sexually risky behaviour as well as high-risk populations, including men having sex with men and HIV-positive subjects, will further reveal the effect of STIs on male genital disorders.

Strategy Flexibility Penned for Younger Men with High-Risk Prostate Cancer after Surgery

SURVIVAL chances of patients who have undergone radical prostatectomy (RP) for prostate cancer (PrC) may be determined by the age of the patient and the time survived post-operation. PrC appears to be the main cause of death in the first 10 years after RP in younger patients, whereas death from other causes takes the lead after

that period, implying the need for a comorbidity profile reassessment after 10 years post-RP.

The EMPACT group was formed to perform a multi-institutional, conditional survival analysis of the long-term outcomes for patients classed as having 'high-risk' PrC and treated with RP, and its findings were presented at the EAU15 conference. The group constructed a database of 7,650 subjects from 14 separate tertiary care centres in Italy, the USA, France, Belgium, Germany, Poland, Switzerland, and the Netherlands. A total of 612 subjects treated with RP across a 26-year period (1987-2013) who were under the age of 60 were recognised in this group, with a median follow-up time of 89 months, and for every subject the number of cancer-specific related deaths (CSM) in the population was recorded and compared with the number of non cancer related deaths (OCM).

The probability of dying from PrC in subjects <60 years of age was found to be higher than that of other causes within 10 years after RP operation; for those who survived 5 and 8 years post-surgery, the rates of CSM and OCM in the next 5 years were 7.3% and 6.7% versus 2.6% and 5.8%, respectively. However, the probability of dying as a result of other conditions overtakes cancer-related deaths following the 10-year period, with CSM and OCM rates within the next 5 years measuring 5.3% versus 9.9%; this suggests that care for these patients should slowly shift from prioritising PrC to prioritising other health hazards such as heart disease.

Participants representing

117

countries

Dr Marco Bianchi, lead author and Professor of Molecular Biology, San Raffaele University, Milan, Italy concluded: "What this means in practice is that each patient needs close, personalised, regular monitoring, where the urologist should not focus only on PrC features, but also on the general health status of the patients. This is particularly important, especially with increasing time after surgery, since new comorbidities such as heart disease may develop and become a more immediate risk to the patient's health."

Erectile Dysfunction after Radical Prostatectomy

ERECTILE function rarely returns to baseline after radical prostatectomy (RP), revealed a study presented at EAU15.

The removal of the prostate gland during prostate cancer (PrC) surgery is often a highly effective treatment option for malignancy, yet it can also lead to a major potential side-effect in the form of erectile dysfunction. The nerves surrounding the prostate are often damaged during the surgery, which can impair erection, and while in many cases this improves over time, research now indicates that achieving an erection of the same quality as before surgery is rare.

The standard process for measuring erectile function comes in the form of a questionnaire: the International Index of Erectile Function (IIEF), but it is not specifically aimed at PrC patients. Arguably, the IIEF does not account for the special circumstances of a sudden change in erectile function brought on by surgery, or allow comparison with sexual activity prior to the procedure.

Researchers led by Dr Mikkel Fode, Department of Urology, Roskilde and Herlev Hospitals, Roskilde and Herlev, Denmark, asked 210 patients to complete the IIEF questionnaire, around 23 months after RP. However, they added an additional question: 'Is your erectile function as good as before the surgery? (yes/no)'.

Thus, while 49 patients (23.3% of respondents) showed no decline in their IIEFF score from before their surgery, only 14 patients (6.7%) reported that their erections were as good as before surgery.

"The occurrence of sexual dysfunction after PrC surgery is well known but our method of evaluating it is new. What this work shows is that having an erection as good as before surgery is a rare event, with the vast majority of men, more than 93% in our sample, experiencing some sexual problems after PrC surgery. Fundamentally, we may have been asking patients the wrong question, but of course we really need bigger trials to confirm this. We think that this work gives a more realistic idea of the real problems which most men have after prostate surgery," said Dr Fode.

The implications of this study are numerous, the most obvious being the need for revision of the IIEF, but these results also suggest that more effort is needed to provide nerve-sparing techniques and improve post-operative care for patients, in order to help prevent these debilitating complications.

Smoking Doubles the Risk of Prostate Cancer Recurrence after Radical Prostatectomy

PHYSICIANS striving to encourage men to stop smoking after being diagnosed with prostate cancer (PrC) have received a boost to their cause from a new study showing that smoking doubles the risk of biochemical recurrence following radical prostatectomy (RP).

Researchers from Europe and the USA performed a retrospective analysis of 7,191 men treated with RP for PrC between 2000 and 2011, and compared the risk of biochemical recurrence (defined as an increase in prostate-specific antigen) between patients classified as 'never smokers', 'former smokers', and 'current smokers'. Multivariate Cox analysis revealed that, after a median follow-up of 28 months, patients who were 'current smokers' displayed at least double the risk of biochemical recurrence compared with 'never smokers' (HR: 2.26, 95% CI: 1.83–2.80; p<0.0001), and the increase in risk was similar when 'former smokers' were compared with 'never smokers' (HR: 2.03, 95% CI: 1.63–2.53; p<0001). However, patients who had stopped smoking for at least 10 years displayed a risk similar to 'never smokers' (HR: 1.20, 95% CI: 0.86–1.68; p=0.29).

These data should hopefully serve as extra motivation for patients who receive a diagnosis of PrC to stop smoking, and more widespread cessation should help reduce the impact of the disease in Europe: it was the third most common cancer diagnosed in men and was responsible for more than 92,000 deaths (9% of all male deaths) in 2012.

The lead researcher, Dr Malte Rieken, University Hospital of Basel, Basel, Switzerland, summarised the study's findings at the EAU15 conference: "This is a new analysis, but it seems to confirm results we have seen in many other types of cancer: basically, smoking increases the risk of cancer recurrence after initial treatment. PrC mortality varies widely throughout Europe. The fact that cancer recurrence can vary so dramatically due to smoking is probably one of the factors which may contribute to differences in PrC mortality. It is just another reason not to smoke at all, but the fact that the risk drops after 10 years means that anyone who has PrC, would be well advised to quit immediately."

Huge Financial Costs of Incontinence Following Prostate Cancer Treatment

FINANCIAL costs for men suffering from incontinence following prostate cancer (PrC) treatment have been laid bare after a study showed that dealing with the disease leaves a huge economic burden for patients, as well as causing emotional distress.

A collaborative group of doctors from the University of Nijmegen, Nijmegen, the Netherlands and researchers from a Dutch insurance company analysed data from 2,834 men who had been treated for PrC, and found that each incontinent man spent an average of €210 every year (range: €112–€283) on absorbent pads. Men suffering from incontinence in the first year after a urological operation or follow-up ranged from 8% for those undergoing conservative treatment ('watchful waiting/ active surveillance') to a colossal 80% for those undergoing laparoscopic surgery (removal of the prostate via keyhole surgery).

"The work also confirms the extent of the problem of incontinence after PrC treatment. Given the size of the problem, we need to attach increasing importance to making sure that patients are not treated unnecessarily, while at the same time missing as few real cancers as possible."

Lead researcher Dr Maarten de Rooij, Department of Radiology/Nuclear Medicine, Radboud University Nijmegen Medical Centre, who presented the group's findings at the EAU15 Congress said: "It can be very distressing to suffer from incontinence and erectile dysfunction after a cancer operation. Our work shows that, on top of this, it can have real economic costs as well – an average of €210 per person in our study in the first year. These are continuing costs for many men whose incontinence does not improve over time. In the Netherlands for example, this side-effect of PrC treatment could cost up to €800,000 per year for only the newly treated men, and we would guess that other countries would have similar costs in proportion to their population.

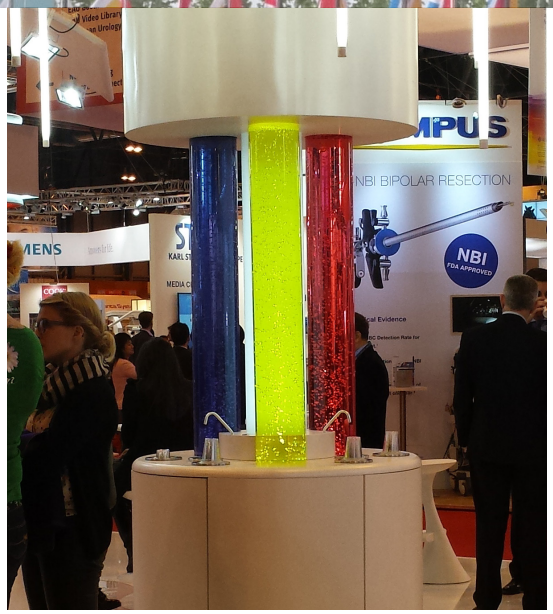
"The work also confirms the extent of the problem of incontinence after PrC treatment. Given the size of the problem, we need to attach increasing importance to making sure that patients are not treated unnecessarily, while at the same time missing as few real cancers as possible."

PrC is the most common cancer in men, with around 360,000 new cases every year in Europe. This highlights the need for further research and funding to look into ways of dealing with the disease, with a view to reducing the devastating economic and emotional impact of incontinence on patients and their families, as well as on society as a whole.

New Survey Reveals Men's Attitudes During Prostate Cancer

DATA showing the attitudes of men who are living with advanced prostate cancer (PrC) have been displayed at the EAU15 Congress, highlighting the most important issues for sufferers and emphasising a need for individualised care.

The *Every Voice Matters* survey, the first and largest of its kind, displayed the results of an in-depth analysis and personal understanding into the lives of 668 men living with PrC across Europe. 75% had localised PrC at diagnosis, 17% had locally advanced disease, and 6% suffered metastatic PrC. Good quality of life (QoL) and a feeling that they were contributing to society were particularly important to many patients: 47% of respondents highlighted that maintaining good QoL, living life to the full, and being able to spend quality time with family and friends were particularly important, in contrast to just 19% who listed being cured as especially significant.



With improvements in the treatment of the disease meaning that more men are living for longer with PrC, there is a need for healthcare professionals to have a greater understanding of lifestyle needs of the patient when discussing treatment options with them, and to further involve the patients in the process. Indeed, the survey showed that while the respondents were generally happy with the communication that they had with their doctor about the disease, there was still a reliance on doctors making treatment choices, with 28% feeling unable to influence their treatment choice.

"This study shows that men with PrC value being able to live life to the full, and this means being able to continue to work, continuing with hobbies, or spending time with loved ones. It is critical that healthcare professionals treat every patient as an individual and take the time to discuss the different treatment options available to agree the best possible treatment plan. By involving patients in treatment decisions and understanding what matters most to them, we can work together to improve QoL for them and their families," said Mr Ken Mastris, Chairman and Board Member of the European Prostate Cancer Coalition (Europa Uomo).

This study is good news for PrC sufferers, who are more likely to have their individual needs met in the future, enabling them to enjoy greater QoL throughout the treatment process.

New Device to Improve the Detection of Bladder Cancer

DETECTION of bladder cancer (BLC) is set to become a much simpler process following outstanding results obtained from the testing of a new device, named the Odoreader, which detects BLC with 93% accuracy through quick gas analysis in urine samples.

"This study shows that men with PrC value being able to live life to the full, and this means being able to continue to work, continuing with hobbies, or spending time with loved ones."

"We have shown that cases of BLC can be identified with great accuracy, by the rapid analysis of gas from urine samples utilising a user-friendly device. The device could be used in screening and surveillance programmes, reducing patient discomfort and costs."

The Odoreader works by reading a unique odour in the urine of BLC sufferers. A heated gas chromatography (GC) column linked to a metal oxide sensor separates volatile organic compounds (VOCs) in a mixture by their mass and/or charge, while the level of the electrical resistance of the sensor changes in the presence of VOCs. The resulting output can then be used to compare the VOC profiles of different sample sets.

The idea for the development of the Odoreader came from a similar method known as gas chromatography/mass spectrometry (GC/MS) that has already shown that diseases can be detected by analysing gases emitted from clinical samples. However, GC/MS has to be undertaken in sophisticated laboratories with appropriately trained staff. The Odoreader in contrast aims to be a much more user-friendly and low-cost device, which provides similar information to the GC/MS but could also be easily applied in a clinical setting.

The Odoreader was used to compare VOC profiles of patients with BLC and a control group in whom no BLC had been previously detected. Two established statistical approaches were used, with correct identification in 100% of cancer patients and 95% of controls in the first approach, and 96% and 93%, respectively, in the second. The developers, Prof Chris Probert and Dr Raphael Aggio, Department of Gastroenterology, University of Liverpool, Liverpool, UK, who presented the findings at EAU15, said: "We have shown that cases of BLC can be identified with great accuracy, by the rapid analysis of gas from urine samples utilising a user-friendly device. The device could be used in screening and surveillance programmes, reducing patient discomfort and costs."

BLC is common, with >10,000 new cases diagnosed annually in the UK, half of whom will die from the disease. This means that the ability of the Odoreader to detect the disease in such a simple and cost-effective manner will be a great boost to health providers worldwide.

Hexvix®-Guided TUR-BT Posts Best Survival Rates in Bladder Cancer Patients

OVERALL survival (OS) and recurrence-free survival (RFS) have been found to be significantly improved in bladder cancer (BLC) patients after radical cystectomy (RC) using Hexvix® (hexaminolevulinate [HAL])-guided bladder tumour resection (TUR-BT) compared with resection conducted with standard white light (WL).

Dr Georgios Gakis, Associate Professor, Department of Urology, Eberhard-Karls University, Tübingen, Germany and colleagues evaluated the medical histories of 224 BLC patients who underwent RC to observe what type of TUR-BT they had previously experienced; 66 (29.5%), 23 (10.3%), and 135 (60.2%) patients had received HAL-guided, 5-aminolevulinate (ALA)-guided, and WL-guided TUR-BT, respectively. 3-year OS and median 3-year RFS were 74.0% and 83.9%, 60.9% and 74.5%, and 56.5% and 59.7% in patients with HAL-TUR-BT, ALA-TUR-BT, and WL-TUR-BT, respectively. Therefore, it was revealed for the first time that HAL-guided TUR-BT appeared to greatly boost both 3-year OS and median 3-year RFS compared with ALA-guided and WL-guided TUR-BT.

"The results of this analysis suggest that an upfront optimised management of patients with BLC might be as critical for outcomes as the prognostic effect of standard pathologic risk factors, especially for those who will progress to advanced disease. To my opinion, the most conclusive rationale for the data presented in our study is improved patient management with HAL-TUR-BT which can make a difference in outcomes even for those patients who display advanced disease at RC," said Dr Gakis, who presented the findings at the EAU15 conference.

Hexvix® allows improved detection and resection of extra tumours through an enhanced visual contrast between benign and malignant cells. Once in contact with the bladder mucosa, Hexvix® infiltrates rapidly proliferating cells and causes a build-up of fluorescent compounds in tumour cells. After 1 hour of instillation, these compounds emit red light and allow specific and accurate visualisation of the tumour. BLC has one of the largest treatment costs per patient of all cancers, due to its highly recurrent nature linked to repeated

treatment approaches in non-muscle invasive BLC. However, HAL-guided TUR-BT has proved capable of minimising recurrence rates, thus reducing overall treatment costs.

"We, as urologists need to focus more on improved BLC management right from the beginning of the disease which may pave the way towards improved BLC outcomes even for those patients who harbour advanced disease at initial diagnosis," Dr Gakis added.

Metabolic Syndrome and Lower Urinary Tract Dysfunction, Linked?

CONFIRMATION of a potential link between lower urinary tract dysfunction (LUTD) and the signs and symptoms of metabolic syndrome (MetS) could aid physicians in identifying and treating more patients with these conditions, according to a summary of clinical evidence presented at EAU15 by Prof Jan-Erik Damber, Chief Physician, Department of Urology, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden.

"In our view, men concerned about their urologic health should be informed about these findings, although definitive knowledge of the associations between MetS and LUTD needs further research."

The societal impact of MetS is difficult to overestimate: approximately one-third of adults in countries where a 'Western lifestyle' predominates are affected. The physiological mechanism underlying its development is a defect in insulin-mediated glucose uptake, which leads to insulin resistance in tissues and secondary hyperinsulinaemia. In turn, these metabolic aberrations increase the risk of diseases and conditions associated with MetS, such as Type 2 diabetes, obesity, hypertension, and dyslipidaemia.

The insulin resistance present in MetS leads to an increase in sympathetic neural activity as well as having a trophic effect on the prostate gland, which can lead to benign trophic hyperplasia. Several clinical aspects of MetS have been associated with an increased risk of overactive bladder, although evidence of a link with MetS overall remains sparse. The development of lower urinary tract symptoms (LUTS) affects approximately one-third of older men. Evidence for an association between MetS and LUTS is inconsistent, with an alternative possibility being that stress-related conditions affecting the sympathetic nervous system underlie the pathophysiology of LUTS. Studies investigating the potential relationship between MetS and prostate cancer have reported conflicting results in this respect.

Prof Damber suggests that physicians treating men with LUTD should consider that some may also manifest some aspects of MetS, and vice versa. Given the uncertain nature of some of the reported associations between MetS and LUTD, Prof Damber suggests: "In our view, men concerned about their urologic health should be informed about these findings, although definitive knowledge of the associations between MetS and LUTD needs further research."

An important implication of confirming such a link would be that treatment of the underlying insulin resistance/metabolic aberrations present in MetS may confer therapeutic benefit to LUTD patients and offer a new avenue of investigation for reducing the morbidity associated with this relatively common condition.

Treatment of Non-Obstructive Azoospermia with Varicocele

TESTICULAR sperm extraction (TESE) combined with intracytoplasmatic sperm injection (ICSI; TESE-ICSI) is a common treatment for non-obstructive azoospermia (NOA), and provides positive results even in cases where only small amounts of sperm canbe collected from testicular biopsies. The presence of varicocele can impair spermatogenesis but varicocelectomy can reverse this, with post-operative data demonstrating a significant decrease in sperm DNA fragmentation. However, the benefit of varicocelectomy in men with NOA

"There seems to be a benefit of varicocele repair for patients with NOA. Varicocelectomy may result in appearance of spermatozoa in the ejaculate. Also, varicocele repair prior to TESE may enhance sperm retrieval."

and cryptozoospermia remains controversial, with some studies reporting a relapse to an azoospermic state or only irregular recovery in spermatogenesis 6-9 months after varicocelectomy.

Simultaneous TESE, cryopreservation of retrieved testicular sperm, and diagnostic testicular biopsy comprise a treatment algorithm for patients with NOA, clinical varicocele, and 'normal' results from genetic screening, whereas patients displaying early maturation arrest or Sertoli cell-only histology can only be treated with TESE-ICSI if sperm were retrieved during testicular biopsy. This algorithm has been contested in NOA because a single biopsy may not reflect the heterogeneous nature of the testicular histology in this condition.

With regards to cryptozoospermia, Dr Marij Dinkelman-Smit from the Department of Urology, Erasmus Medical Centre, Rotterdam, the Netherlands, suggested at the EAU 2015 congress in Madrid that this controversy can only be addressed in patients with cryptozoospermia through randomised clinical trials that directly compare varicocelectomy with no intervention, and that include multiple semen samples taken before and after randomisation.

Dr Dinkelman-Smit acknowledged that treatment of NOA and cryptozoospermia is practically challenging: "Patients and their partners will need to refrain from upfront TESE-ICSI using cryopreserved testicular sperm to embark on varicocele repair with unclear outcome." Dr Dinkleman-Smit also concluded: "There seems to be a benefit of varicocele repair for patients with NOA. Varicocelectomy may result in the appearance of spermatozoa in the ejaculate. Also, varicocele repair prior to TESE may enhance sperm retrieval."

Recurrent Urinary Tract Infection and Antibacterial Resistance

TREATMENT of recurrent urinary tract infection (rUTI) must be more effectively stewarded so as to avoid a wealth of negative complications, according to a summary of clinical research presented at EAU15 by Prof Robert Pickard, Professor of Urology, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.

Affecting women all over the world, rUTI is a health problem with an approximate prevalence of 120 cases per 100,000 individuals. The symptoms of rUTI, while not fatal, can impact on all aspects of daily life, making it an extremely debilitating condition; thus, there is much clamour for effective solutions. The most commonly used treatments are antibiotic prophylaxis or self-start short-course antibiotic therapy.

However, there is growing concern both in the medical community and among patients over the unwanted side-effects of antibiotic overuse.

12,000 participants

Uropathogens such as *Escherichia coli* can easily develop resistance to antibiotics, and the occurrence of their resistant forms is increasing worldwide. Prof Pickard argued that there is much to do to combat the spread of infections caused by multidrug-resistant pathogens: "Misuse and overuse of antimicrobials is one of the world's most pressing public health problems. All urologists must respond to the problem chiefly by having knowledge of and consistent application of relevant clinical guidelines."

Adherence to such guidelines is part of what Prof Pickard refers to as antibiotic stewardship, a co-ordinated programme whereby urologists must carefully monitor antibiotic use, reducing or avoiding its application where possible. However, while this practice is effective in fighting antibiotic resistance, alternative treatment options for rUTI must be pursued. One solution Prof Pickard offered is via the betterment of diagnostic techniques, which could expedite the prescription of specialised antibiotics, as opposed to broad-spectrum treatments that are more likely to foster resistance. "A number of new agents within existing classes of antibiotics are under trial but are likely to suffer the same fate in terms of *E. coli* resistance as existing members of each class," added Prof Pickard.

The most promising avenue of treatment arguably lies in the

innate immune system, which can be harnessed to heighten the immune response to uropathogens, helping the body to fight infection. Ultimately Prof Pickard advocated the essential education of patients and practitioners regarding the long-term dangers of misuse and overuse of antibiotics.

Antibiotic Resistance Diminished by Adherence to EAU Guidelines

SURGICAL methods have been subject to change in the past 5 years as scientists attempt to prevent bacterial resistance to antibiotics and reduce medical costs, while continuing to protect against infection.

With a lack of antibiotics in development, antibiotic resistance currently poses a serious healthcare problem. By changing the way that these drugs are used it is hoped that antibiotic resistance-associated issues may be contained.

That was until 2011 when a group of international clinicians participated in a multi-centre study, which demonstrated that adherence to new guidelines implemented by the European Urological Association (EAU) in 2010 can significantly reduce bacterial resistance in urological surgery.

In order to test how effective urological surgeries were under the new guidelines, the team measured the outcomes of 3,529 urological procedures performed under strict adherence to EAU Guidelines. Comparing their results with 2,619 similar operations from 2006-2008, they discovered that, although the rate of infections was similar in the two periods, the overall costs (including those of antibiotic drugs) and antibiotic resistance rates were greatly reduced; for example, in the period before the 2010 guidelines cost-per-procedure was €46.90, but this dropped by 60% when working within the guidelines to €18.77.

Prof Robert Pickard, Professor of Urology, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK, and Chair of the EAU Guideline Panel on Urological Infections at EAU15 Congress summarised the findings of the team:

"The main bacterium that causes all types of urinary infection, *Escherichia coli*, is becoming increasingly resistant to treatment using the antibiotics we have available in 2015. This antibiotic resistance is a major health threat, particularly to countries in the EAU community with our advanced healthcare systems. The only proven way to reduce the threat is by antibiotic stewardship to control the overuse and misuse of antibiotics in healthcare. This study shows that by following a few simple rules hospital usage of antibiotics can be dramatically reduced without affecting patient safety, and results in lower resistance and reduced costs."

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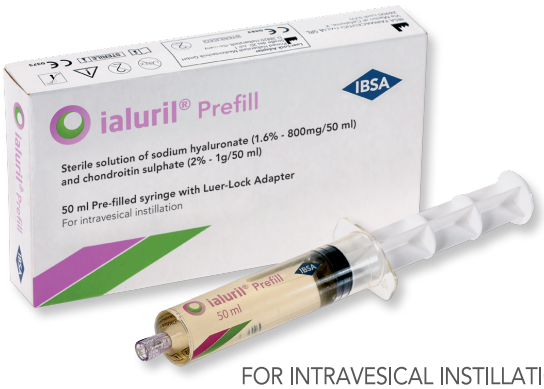

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3. Giberti C. et al. 2013 - 4. Damiano R. et al. 2011 - 5. De Vita D. et al. 2012

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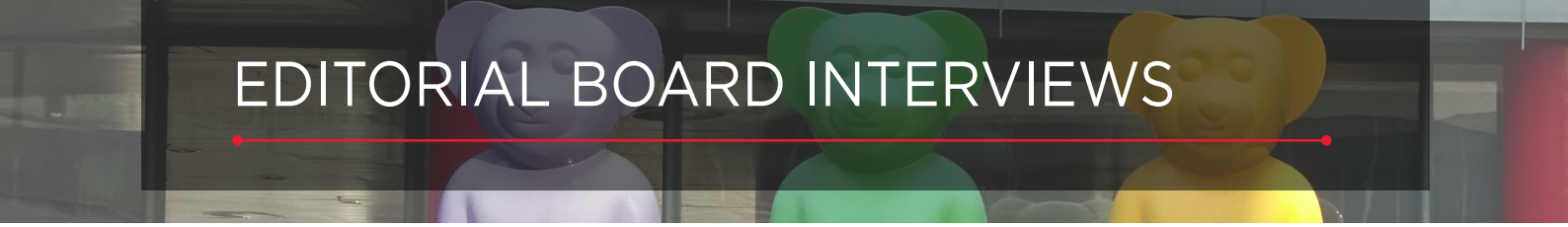

Evangelos Liatsikos

Associate Professor of Urology, Head of the Endourology-Laparoscopic Unit, and Director of Endourology Fellowship Programme, University of Patras, Patras, Greece; Visiting Professor, Department of Urology, University of Leipzig, Leipzig, Germany.

Q: As an expert in laparoscopy and other minimally invasive techniques, how would you describe the pace of development in this field?

A: During the last 10 years a tremendous evolution of minimally invasive techniques in urologic surgery has taken place. Many concepts previously considered experimental are currently being employed as gold standard approaches, including laparoscopic partial nephrectomy and clampless kidney surgery. In addition, mini-laparoscopic approaches using even smaller laparoscopic instruments, laparoendoscopic single-site surgery (LESS), and transvaginal specimen extraction have been introduced in an attempt to further reduce laparoscopic morbidity. Robotic assistance is leading the way in minimally invasive surgery as its superiority over conventional laparoscopy in terms of 3D vision and improved degrees of instrument freedom have boosted the diffusion of this technology worldwide, and today the majority of radical prostatectomies performed in the USA and in some European centres are performed with robotic assistance.

Q: How has the increasing use of robotic assistance and advanced imaging software impacted upon the application of laparoscopy on a day-to-day basis?

A: Improved high-definition and 3D imaging, as well as robotic assistance, have provided the tools for laparoscopic surgeons to perform even more complex operations with improved outcomes. The latter is evidenced not only in laparoscopic operations replicating the standards of open surgery, but also in laparoscopic operations being established as the new gold standard in providing excellent oncological and functional results with decreased morbidity.

> "Ureteral stents are a very important tool in the management of a variety of benign and malignant pathologies."

Q: How would you describe the current uptake of LESS amongst nephrology and urology units both across Europe and internationally, and what are the greatest challenges to clinical teams wishing to apply this technique?

A: LESS is a novel concept in laparoscopic surgery that in its current form is characterised by significant drawbacks such as instrument classing and in-site view that limit its diffusion among urologists. The concept of introducing all necessary instruments by a single access has a steep learning curve that should be expected by all clinical teams embarking on the technique. Nevertheless, there is an ongoing evolution of instruments, the most important being the development of robotic single-site platforms. This will eventually provide urologists with the armamentarium to successfully employ LESS without its current limitations and it could potentially replace conventional multiport surgery.

Q: Another focus of your work has been the ongoing development of ureteral stents – how has this technology developed during your time in the clinic?

A: Ureteral stents are a very important tool in the management of a variety of benign and malignant pathologies. During the years I have been a urologist, I have witnessed a parallel evolution of ureteral stents with endourology. Currently, there is a great variety of stents incorporating different stent designs and biomaterials with various characteristics indicated for each particular disease. Still, the ideal stent is missing, as most of these stents demonstrate drawbacks and adverse reactions including migration,

encrustation, obstruction, and development of stent-related symptoms. Thus, novel biomaterials and stent platforms are still under intensive investigation, and keeping up with developments in this field has been and will continue to be a very exciting area of interest.

Q: In your opinion, what is the greatest current challenge faced by nephrologists and urologists in Europe today, and how can we best begin to address this?

A: Novel treatments employing modern instrumentation are often expensive, and as economical resources are not unlimited, one of the greatest challenges for modern urologists is how to provide the less expensive and cost-effective state-of-the-art treatment to patients in a way that would not compromise the outcomes that modern urology can offer. This cut-off point is not very easy to address, and urological associations should offer guidance to all practicing urologists on what is acceptable and what is not, among a constantly expanding field of novel instrumentation and treatment options.

Q: Could you speculate on what is likely to be the 'next big thing' in the field of laparoscopy, and how long do you imagine it will be before this is introduced into clinical routine?

A: I would expect that the next generation of robots in urology will be the next big thing. Current application of robotic technology is characterised by excellent and convenient feasibility at the cost of an increased price. Reducing the cost of robotic surgery could be what is needed for the complete replacement of conventional open and laparoscopic operations. I would expect that the next generation of patients worldwide will only be operated on with robotic assistance.

Q: With regard to the latest manuscript that you submitted to our journal, which observed the effectiveness of laparoscopic radical prostatectomy (LRP) in comparison to robotic-assisted radical prostatectomy (RARP) in treating prostate cancer (PrC), you concluded that a conventional LRP approach was still favourable due to the high financial cost of RARP, although the integration of novel laparoscopic instruments into LRP was necessary in order to address its drawbacks. Do you believe that there has been sufficient progress in terms of adapting LRP to combat such drawbacks since the publication of this article?

A: Laparoscopy is currently employed as the gold standard minimally invasive approach where there is an absence of robotic assistance. Wherever a robotic surgical system has been installed, there is a trend of superiority in terms of the surgeon's covalence and intraoperative dexterity, when compared with conventional laparoscopic surgery. Still, as mentioned before, robotic-assisted surgery in its current form is too expensive to be provided worldwide. As a result laparoscopy is still largely employed throughout the world, even if its drawbacks have not been universally addressed.

Q: With the high cost of RARP reducing its accessibility to patients suffering from PrC, how long do you think it will be until robotic technology will become more cost-effective? And are there any policies that you think governments could undertake to make this happen more quickly?

A: As with all technologies, there is a long gap between product development and widespread use. Still, I think that a number of companies have long been on the way to developing novel robotic platforms, and the competition offered by the introduction of new products is what is needed to reduce robot prices. Governments have all the tools required to promote competition in this expanding field of medicine.

Q: What advice would you give to men in order to reduce their chances of developing PrC?

A: I think that there is no real advice anyone could be given to avoid PrC. The most significant risk factor for developing this neoplasia is age and by the age of 80 most men have a form of prostatic malignancy. Still, the vast majority of them are asymptomatic and PrC will be something they will die with but not from. As a result, advising against developing PrC is similar to advising against ageing. On the other hand, we currently cannot predict with certainty the course of this malignancy in a particular patient in terms of not being able to distinguish those who will undergo an uneventful course and those who

will develop metastases and eventually die from PrC. Summing up, I would not advise on how to avoid PrC development but I would definitely advise an increase in PrC awareness. The latter should be translated into following the guidelines for PrC screening in an effort to recognise those cancers with an aggressive potential early, and to treat them early.

Q: How have our understanding and treatment of PrC developed since you first began working in the field?

A: Our understanding and treatment methods in PrC have seen many changes over the last few years. We have seen a move away from population-based intensive PrC screening and have widened the employment of active surveillance for low-grade PrCs. In addition, surgical management of advanced disease was reinforced in parallel with the introduction of multimodality treatment protocols. Finally, our understanding of PrC hormone-sensitivity has led to the development of novel agents to benefit patients with castrate-resistant PrC.

Q: Do you see yourself branching out into new areas of urological research in the future, or do you think that there is still much to observe within your current main areas of research, such as laparoscopic surgery and ureteral stents?

A: I am always open to new ideas of urological research; however, I mostly apply new areas of interest into my field of expertise. Based on my experience, a combination of different areas of scientific interest is the key to the development of the most exciting outcomes. The best way to describe this is to imagine that each investigator is looking at the same picture through a small hole of interest; only if we combine our knowledge can we reveal the whole picture.

Murat Arslan

Associate Professor of Urology, Department of Urology, School of Medicine, Izmir University, Izmir, Turkey.

Q: At what point during your medical studies did you decide to specialise in the field of urology, and what was the reason for this?

A: I decided to be a urologist in my 4th class of a urology internship, with the great contribution of Prof Orhan Yurtseven. I was very impressed by endourology. I realised that there are enough orifices in the human body through which one can perform operations, but we had been forced to undertake surgery using large incisions because of the technological barriers at play.

"Younger surgeons are able to complete their laparoscopic training faster by doing virtual training operations using these robotic training programmes."

Q: As an expert in laparoscopy and other minimally invasive techniques, how would you describe the pace of development in this field and how big a role do these techniques play in the management of urinary tract stone disease?

A: There have been incredible technological advances in endourology over the past 20 years. While Endo Vision equipment and techniques were of a low quality when I started to perform laparoscopic operations with three or four incisions, today we have a chance to do the same operations using umbilical laparoendoscopic single-site surgery due to improvements in 3D and HD systems, as well as bend-hand equipment. Application of these technological developments in urolithiasis was realised using flexible ureteroscopy (URS). Imaging has developed with the help of flexible URS with a digital system.

Q: How has the increasing use of robotic assistance and advanced imaging software impacted the application of laparoscopy on a day-to-day basis?

A: While many urologists were previously hesitant to perform laparoscopic surgeries, due to the steep learning curve, this has been reduced with the help of robotic surgery and laparoscopic procedures are now more popular.

Q: How has the increasing use of technology affected the training that young urologists receive?

A: Virtual pelvic trainers have been introduced and many surgeries have started to operate in training boxes within a virtual environment. Younger surgeons are able to complete their laparoscopic training faster by doing virtual training operations using these robotic training programmes.

Q: Most people associate urinary tract stone disease with older patients - how common are these conditions in children and are any specific groups at greater risk?

A: While urolithiasis is seen most frequently in the 20-40 years age group, the risk of urolithiasis in childhood has started to increase in recent years. According to researchers, this situation is related to the consumption of salty foods and an increase in the consumption of water.

Q: How does the treatment of these conditions differ between adults and paediatric patients?

A: Urinary stones (calculi) occur commonly in adults, but less often in children. Because of this, there is less known about the treatment of stones in children. The incidence of calcium stones in adults is high, with the minority having a significant metabolic abnormality. In children, stone formation is less common and, therefore, one is more likely to find an underlying metabolic or anatomical abnormality in children who develop stones. Many of the children who develop urinary stones have an underlying abnormality of the urinary tract. These include obstructions of the kidney or ureter, and diseases such as spina bifida and bladder exstrophy. These anatomical problems make the treatment of stones in children more complicated and require that any treatment be given in conjunction with a paediatric urologist. Most kidney stones in children can be treated with extracorporeal shock wave lithotripsy (ESWL); this is a cutting-edge treatment for urinary stones. The impact of ESWL on the developing kidney has not been established beyond doubt, but it seems from many large studies that this is a well-tolerated and effective way to treat paediatric kidney and ureteral stones. Although some forms of ESWL can be given to adults without anaesthesia, most children require at least sedation to keep them calm and to keep them from moving, so that focus on the stone can be maintained. The more powerful forms of ESWL are painful and children require anaesthesia for this reason. Endoscopic approaches are most useful in these situations. These techniques were developed for the removal of stones in adults and were used, for the most part, without modification in children. A few groups have tried to downsize the instruments to make them more appropriate for children, but these efforts have been sporadic. Recently, the technique referred to as 'mini-perc' was specifically designed for paediatric percutaneous nephrolithotomy, and has also been applied in adults, allowing removal of kidney and ureteral stones through a small puncture.

Q: Could you speculate on what is likely to be the 'next big thing' in the treatment of urinary tract stone diseases, and how long do you imagine it will be before this is introduced into clinical routine?

A: Urine dilution, alkalinisation, and chelating therapy have remained the cornerstones of the therapeutic approach. The importance of a low urine pH has been further emphasised, and the possibility of using alpha blockers is a promising improvement to the treatment outcome. In order to increase compliance and reduce the need for stone removal, specialised stone clinics seem to be of particular value. Understanding the influence of genetic background might lead to future treatment alternatives.

Q: Another of your clinical interests is uro-oncology. How have the detection, treatment, and prognosis of prostate cancer and bladder cancer evolved during your time in clinical practice?

A: Laparoscopic and robotic surgery options have allowed a tremendous leap in treatment by decreasing the blood loss and the duration of stay following hospitalisation. Also, positron

emission tomography (PET) and magnetic resonance imaging (MRI) increasingly help to identify metastases.

Q: Are there any preventative measures that can be taken in order to avoid urological health issues, both in children and adults?

A: In order to avoid such issues, one should take part in disease screening, identify risk factors for disease, discuss tips for a healthy and balanced lifestyle, stay up-to-date with immunisations and boosters, and maintain a good relationship with a healthcare provider.

Q: Do you have any advice for young doctors, either already in the field or hoping to start out on a career in urology?

A: Urology is ideal for young doctors because there is a chance to apply all kinds of approaches such as laparoscopic surgery, robotic surgery, and endourology by utilising technological advances. I predict that urology will be at the forefront of closed surgery, using only natural orifices to perform procedures. My advice to young doctors is to increase their experience in endourology and complete their education in the robotic and laparoscopic fields.

Q: Are there any areas of urology clinical practice or research that are particularly interesting at the moment, or areas of development that will be covered at EAU 2015?

A: I am looking forward to hearing about the new technological developments in the endourology field. Hopefully the following questions concerning urologic cancer staging will be answered: i) How useful and valuable are PET-CT and PET-MRI when evaluated in controlled studies? ii) What are the new generation of medicines in chemotherapy for kidney cancer? iii) What are the results of genetic therapies in kidney and bladder cancer?

> "Laparoscopic and robotic surgery options have allowed a tremendous leap in treatment."

Jean de la Rosette

Jean de la Rosette is Chairman, Department of Urology, Academic Medical Center (AMC) University Hospital, Amsterdam, the Netherlands.

Q: What are your main fields of interest?

A: My main field of interest is endourology in adults. My involvement in treating children is related to urinary stones.

Q: Are urinary stones a common concern in children, and how well is your expertise suited to their treatment?

A: Urinary stones in children are seen at our department increasingly given the fact that we are a specialised centre in treating (complicated) cases with urinary stones. Since endourologists are experts in treating the larger number of adults with urinary stones, they are also the logical experts for treating urinary stones in children.

Q: If urinary stones go unnoticed or are left untreated, what implications can this have on the growing child in later life?

A: Urinary stones are often diagnosed early because of complaints of pain or urinary tract infections. If not treated, impairment of renal function may occur, resulting in a poor renal function that requires renal replacement therapy such as dialysis or renal transplant.

Q: Are there any significant differences between the ways in which you treat children with urological issues and adults with the same problems conditions?

A: When treating children with urinary stones, the technical requirements are often the same, but

this is not just about treating a smaller person. Children are more fragile and minor complications can have a major impact. Moreover, the parents are often strongly involved in the management and this requires special skills. Having said this, at our hospital, a close collaboration between the paediatric urologists and the endourologists safeguards the optimal treatment. The paediatric urologist is the co-ordinating specialist, communicating and co-ordinating all activities related to the treatment of children with urinary stones.

Q: What are the most common adult urological problems that you see in the clinic?

A: For adults we have two main topics: oncology and endourology. There is a close link between both super-specialties because, for example, bladder tumours are often treated by endoresection. In more progressed cases, a more sophisticated oncological treatment is required. In general, we see a large proportion of patients with renal, prostate, and bladder cancer from the oncological point of view, whereas in endourology we see many cases of urinary stones and benign prostatic hyperplasia (BPH).

Q: Being overweight often brings with it additional health issues. Does the fact that Europeans are becoming increasingly overweight have any impact on the number and severity of urological problems seen by practitioners?

A: Yes and no. In general, being overweight results in a higher risk of developing cancers and can also be a cause of metabolic syndrome, resulting in a higher risk of urinary stone formation and BPH.

Q: Are the incidence and prevalence of renal tumours increasing?

A: Definitely. In 2010 we were treating 10 new cases of renal tumours per year, whereas right now we are seeing 125 new cases each year. This is, on the one hand, related to the special expertise of our centre, whereas, on the other, the prevalence in general has increased. This increase is especially true for the presence of so-called small renal masses.

Q: Are there any further implications of renal tumours in elderly patients, i.e. do they cause other health problems in themselves?

A: Elderly patients are often more fragile and treatment of their condition may cause significant morbidity. Since the renal function in elderly patients is often somewhat impaired, renal insufficiency may occur as a consequence of the treatment of a renal tumour. This has major implications for their wellbeing and (especially) their quality of life. It has been demonstrated that a nephrectomy confers a higher risk of hypertension, cardiovascular incidents, and eventually death.

Q: Are there any preventative measures that can be taken in order to avoid urological health issues, both in children and adults?

A: As mentioned before, obesity is a major concern and lifestyle advice is easily available, which should result in a direct effect on health. During the follow-up, we should advise the patient community to adopt a healthy lifestyle.

Q: Are there any recent advancements in technology that have revolutionised the way you treat, or have made the management and treatment of urological conditions easier and more cost-effective?

A: The introduction of smaller endoscopes has revolutionised the treatment of urinary stones. At present, there is an increasing trend to treat the vast majority of urinary stones by retrograde intrarenal surgery. For oncology, the introduction of the da Vinci robot has changed the surgical management of tumours. This is becoming the major tool to surgically treat oncological conditions, with favourable outcomes for both patients and doctors. The latter operate in good ergonomic conditions resulting in less physical harm to the patient's body.

Q: If so, how have these benefitted healthcare workers and/or patients?

A: The treatment is less invasive, faster, and thus results in a faster recovery for the patient.

"The introduction of the da Vinci robot has changed the surgical management of tumours."

"EAU provides great educational platforms..."

Q: Is there still a place in urological practice for more invasive forms of surgery?

A: All open surgery is invasive. The position of open surgery has been reduced significantly and is performed by expert surgeons for the treatment of complicated conditions.

Q: How does the practice of your colleagues in the developing world differ from your own in Europe? Do they encounter a different set of diseases? Without the advanced technologies that we have access to, do the ways in which they treat patients differ dramatically?

A: Colleagues in the developing world are rapidly catching up since they also have increasing access to new technologies. Their scenario is different from ours in the case of the vast number of patients that present with a major focus on urinary stones and BPH. Oncological conditions are still less prevalent, but with the increase of wealth, there is also an increase in the demand for better healthcare services.

Q: What drew you to the field of urology?

A: I was fascinated by the different pathologies. When I finished my training, I was invited to further build upon my experience in endourology and minimally invasive technologies. I never regret any moment that I did so.

Q: Have you experienced any cases in your field that have baffled you/been incredibly rare? If so, what did you do to overcome the problem and treat the patient?

A: We see an increasing number of patients with problems of the upper urinary tract who have had surgery before requiring bladder replacement. It is a challenge in these cases to reach the upper tract, either retrograde or antegrade. When mastering those cases, one is really 'on top of the pyramid' of endourological expertise.

Q: What are the next stages for your own research?

A: The 'new kid on the block' is the diagnosis and treatment of upper urinary tract urothelial tumours. Our team has embarked on several interesting research projects to better diagnose and treat these patients conservatively with retrograde intrarenal surgery.

Q: Do you have any advice for young doctors and practitioners, either already in the field or hoping to start out on a career in urology?

A: Invest in research and take part in a network to perform research. This is most rewarding on a personal and professional level and keeps you up to date in the field.

Q: Are there any changes that you would like to see in the field of urology, either on a global scale or on a more personal level?

A: We are facing an increasing demand for administrative work. It would be a relief if this was less so that we could focus on what we are best at: treating our patients to the best of our abilities.

Q: Are there any areas relevant to urology clinical practice or research that are particularly well-covered at EAU?

A: The EAU has become a powerful association uniting urologists from Europe. EAU provides great educational platforms and is reaching out to the next generation to join and take part in all of the activities taking place. Given the variety of urological care, there is an opportunity for everybody to make a choice based on this preference.

Q: Did you present research at EAU this year?

A: I am part of a bigger team that presented at this year's EAU meeting. Our team proudly presented work conducted in close collaboration with other European teams. I also gave podium presentations and moderated sessions; the most important positions were taken by our young researchers and it makes me proud to see them perform with excellence and enthusiasm.

Q: Finally, do you have any overall comments on the field of urology and the advancements that are being made across healthcare settings?

A: The world is becoming smaller and consequently this opens new avenues. We can help each other to learn new approaches, share new insights, and continue to learn with the goal of providing the best quality of care to our patients.

Selcuk Guven

Associate Professor of Urology, Department of Urology, Medipol University, Medipol Mega Hospital Complex, Istanbul, Turkey.

Q: As an expert in laparoscopy and other minimally invasive techniques, how would you describe the pace of development in this field and how big a role do these techniques play in the mana gement of urinary tract stone disease?

A: Endoscopic stone treatment has always been the field of interest since ancient times. In the last decade, technological advancements and refinement of both ureteroscopes and percutaneous nephrolithotomy equipment has facilitated access to the entirety of the urinary tract and management of almost all stones. These developments allow us to approach the treatment of stone disease from a different perspective when compared to open surgery and shock wave lithotripsy (SWL). Today the ureteroscopy experience gained in many clinics has made ureteroscopy a first-line treatment option along with SWL for kidney and ureteral stones. Through endoscopic methods, interventions can be recorded and registered and the technology can be adapted easily. Stone disease, which is frequently recurrent and one of the prevalent motivations of chronic renal failure, is treated without degradation of the patient's anatomy with invasive techniques. Minimally invasive techniques have decreased patient morbidity while preserving high stone clearance rates. Beyond the benefits to patients through endoscopy, technology improves every day and new developments can be adapted more easily to the endoscopy unit.

Q: How have recent developments in computer and imaging technologies impacted not only the application of laparoscopy, but also the teaching and training of this surgical technique?

A: The development of completely pre-programmed, fully automatic surgeries will soon be on the horizon. Although we regularly make use of technological advancements in urological applications, many developments in computer and imaging technology are not yet widespread in routine practice. For now, introducing new surgical technologies to the operating room and the safe instruction of novice surgeons is challenging. Simulation training is an important aide in a surgeon's training in urology. This training includes a wide range of disciplines, such as transrectal prostate biopsy, endoscopic interventions, laparoscopy, and robotic surgery. In this regard, revolutionary developments have occurred in the education of urologists with high-tech surgical simulators. Although a limited number of training centres have this technology, it is not yet accessible to every resident training in urology today. The training principles of Halstedian are supposed to be adapted to the present day, I think we couldn't show success on this point that we show in developing and making use of technology. There is not yet a standard training programme which applies to technology involving whole departments. In order to generate the equality and standard among urologists trained in the endourologic era, it is essential to develop new training policies.

Q: You recently published the results of the CROES global study on the use of percutaneous nephrolithotomy (PCNL) in paediatric patients, what were the main findings from the study?

A: The paediatric PCNL results presented in the aforementioned paper were a part of the global observational study and were a first prospective audit data collection. The CROES database provided the unique opportunity to compare the PCNL results of adult and paediatric cases for the first time. The comparisons made have shown that the complication rates in paediatric cases

were comparable to those in adults. Beyond the outcomes of general PCNL intervention, we saw the application differences between countries, regions, and departments, etc. As we know from the previous reports, PCNL is safe and effective in children and it has been used for more than three decades; the CROES study confirmed most of the results reported previously in the literature. I think the main outcome of the study was that relatively few children were registered to the whole study. As we mentioned in the paper, urologists only dare to perform paediatric PCNL applications after they have gained much experience with adult cases. So the discussion is who should perform PCNL in children? Dedicated paediatric urological surgeons or adult surgeons? It may very well be that the case load per surgeon in general is the most important aspect, and not the age of the patient treated.

Q: Most people associate urinary tract stone disease with older patients - how common are these conditions in children and are any specific groups at greater risk?

A: Stone disease has noticeably increased in the general population by almost two-times in the last two decades. The prevalence of stone disease development throughout life in adults is between 10-15%. Although paediatric kidney stones are encountered rarely, the increasing incidence reported is concerning. Stone disease in children has been reported at around 2-3% but the actual prevalence is a controversial subject. This proportion is higher in some countries. While stone disease is more frequently seen in male adults, female children are more susceptible to nephrolithiasis than male children. Furthermore, infection stones occurrence in children decreases while there is an increase in children's stone disease. Undertaking better management of the metabolic, anatomic, and neurological disorders, the kidney stone infection decreases in children. It is thought that the overall stone disease increase can be attributed to many factors such as obesity, beverage consumption, climate change due to global warming, and the prevalence of Western-type nutritional habits; however, none of these are proven yet. The majority of paediatric stone patients are idiopathic: in 9-24% of patients congenital urinary tract anomaly, metabolic deficiency, or neurologic disease are detected. Unlike adults, in early childhood, approximately 50–60% of stones are located in the kidney at the time of diagnosis, and with increasing age ureteral stones are more common in adults.

Q: How does the treatment of these conditions differ between adults and paediatric patients?

A: Paediatric stone patients are a high-risk group. While comparatively only a small proportion of the patients in urology clinics represent paediatric urolithiasis, the most effective treatment for these patients is of utmost importance. Therefore, metabolic evaluation should be performed in all children. By this means we can not only prohibit the recurrence of the disease in the future, but also purge the stone effectively. In recent literature almost all adult stone disease treatment options are reported to be used for treating children safely and effectively. However, three major concerns among children and adults should be taken into account: i) we ought not to disrupt the development of a growing kidney and its function; ii) we have to minimise radiation exposure in younger patients, and iii) we should minimise the need for retreatment.

Q: Could you speculate on what is likely to be the 'next big thing' in the treatment of urinary tract stone diseases, and how long do you imagine it will be before this is introduced into clinical routine?

A: On this point, we should set apart the basic research from the endourologic management of stone disease. My dream is of the creation of a new generation of targeted therapies to prevent the formation of kidney stones. With the progress of navigation-assisted endourologic methods and, with the greater use of technology, a stone at any point of the urinary system can be found automatically and broken up with flexible optical instruments and lithotripters. Beyond this, fully pre-programmed interventions hold promise in the next decade.

"Endoscopic stone treatment has always been the field of interest since ancient times."

Riccardo Bartoletti

Associate Professor of Urology, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

Q: Your current research focuses on the HPV virus in men as well as women, what led you to this interesting area of study? Were there any particular influences that inspired you in this field?

A: Since 1984 Prof Harald zur Hausen investigated a novel vaccine against human papilloma virus (HPV) infection. Relationships between chronic HPV infection and cervical cancer (CVC) in women had already been demonstrated, as had the possibility of transmitting the infection through sexual intercourse. Many investigators underlined the role of men as a possible carrier of infection for women, but none of them sufficiently investigated the effects of infection in men. Men usually pay less attention to their bodies than women. A clear example of this behaviour can be found in the late diagnosis of testicular cancer, which is often due to infrequent scrotal examination by self-palpation. Conversely, women usually pay a lot of attention to breast self-palpation with the aim of searching for suspected nodules. Medical consultations are frequently instigated by the presence of indolent penile condylomata or the need to investigate a couple's infertility. A lot of men continue to consider penile condylomata to be irrelevant and with scarce implications for sexual activity. Recent studies demonstrate a significant increase in the prevalence of penile, anal, and head and neck cancers due to HPV infection. In men living in developed countries, HPV-related cancers are usually found among specific groups considered at risk of infection, such as immunodeficient patients (due to HIV/AIDS or other non-viral causes) and men who have sex with men (MSM). Moreover, prostate cancer (PrC) and bladder cancer (BLC) are currently considered the first and sixth-most common causes of cancer death in men over 60 years of age. The questions we wanted to answer were: i) Is there a relationship between HPV infection and cancer development, and ii) can male vaccination against HPV be useful in decreasing the risk of transmitting HPV infection and reducing the prevalence of HPV-related cancers?

Q: Your research seeks to reduce the risk of women developing CVC by providing an HPV vaccine to men. If such a vaccine were to be implemented, how long do you imagine we would need to wait before we saw a significant change in the number of women being diagnosed with CVC?

A: A prevention programme with HPV vaccination normally induces a positive impact on the reduction of infections in sexual partner(s), but seems to be strictly related to sexual behaviour. As a consequence the prevalence of HPV infection in men is proportionally related to the degree of sexual promiscuity of both men and women. Bosch et al. demonstrated that the risk of developing penile HPV-related lesions isincreased in men with a wife with multiple sexual partners. On the other hand, the primary prevention scenario in men seems to be extremely complex due to limited knowledge of the natural history of HPV infection, evidence of conflicting results of concordance in the same couple, and the lack of adequate social and health policy on HPV infection. The risk of developing HPV infection-related diseases and equality between genders are other good reasons to promote HPV vaccination in men. Previous studies demonstrated that male HPV vaccination is able to induce an 89.4% decrease in penile condylomata, while Fairley reported a good 'herd immunity' (an indirect positive effect) in male sexual partners of women previously vaccinated for HPV infection. Since 2007 the quadrivalent vaccine has been administered to Australian girls aged 12-18 years and to women younger than 26 years, with a coverage ranging from 65-75%. Just 1 year after the start of the vaccination programme there was a 48% reduction in the rate of diagnosis of condylomata in women younger than 28 years, although not in those who are older. A significant reduction of 17% in the prevalence of condylomata in men has also been found during the same period, except in MSM, which suggests some evidence for herd immunity

in the male sexual partners of women. In the same manner, a vaccination policy aimed at young men may induce similar results in both heterosexuals and MSM.

Q: Alternatively, if things remain the same with regard to the prevention of HPV infection, should we expect to see a dramatic rise in the incidence and prevalence of CVC? What impact would this have on healthcare services and sexual health practitioners?

A: Diagnosis of CVC has increased in recent years due to a significant change in sexual behaviour and the diffusion of sexually transmitted infections (STIs) in both genders despite governments' prevention policies, as well as the introduction of the HPV test as an alternative diagnostic method to the Pap test. On the other hand, the incidence of death due to CVC has decreased during the last 40 years, probably due to the same reasons: improvement of diagnostic methods, earlier diagnosis of cancer, and improved treatments. The worthwhile use of condoms has been evaluated in multiple studies on the prevalence of HPV infection. Baldwin demonstrated a lower risk of HPV infection in men who consistently and continually made use of condoms during sexual intercourse compared with men who only used condoms occasionally. Moreover, different studies have demonstrated multiple pathways for virus transmission, such as skin-to-skin, inappropriately washed underwear and lingerie, and from inanimate objects.

Q: Sex education remains poor in the majority of countries - are there any programmes or movements that are trying to change the provision of sex education, and which you particularly support?

A: Sex education policies should be improved generally in every country in the world. In particular, clear information on the effects of STIs, the presence of sexual abnormalities in males, and the methods that should be used to prevent infections or solve the problems should be scheduled into school-year programmes and presented to young people in collaboration with experts in the field. We have presented an information campaign to high-school students during the last 5 years and found that about 45% of the boys reported previously unrevealed sexual and andrological diseases. Most men have difficult relationships with their own body and most are unable to determine if a sexual problem or a physical sexual abnormality is important or not. Conversely, women have a wide culture describing the topic and pay specific attention to their safety and health. Many of the sexual problems reported by males are discovered by their sexual partner.

Q: We are increasingly told by the media that young people are becoming sexually active earlier. Has this had any impact on the cases that you see in everyday clinical practice? Are the patients you tend to diagnose and treat for both STIs and CVC getting younger?

A: The majority of young people become sexually active early. The median age at first sexual intercourse is 16 years for girls and 17 years for boys. Women commonly report being pressured into their first intercourse, especially those who experience this before 14 years of age, and most women who have intercourse before 16 years of age report that they feel they should have waited longer. More women than men report the occurrence of an STI, especially among those who had intercourse before 16 years of age. This implies an increased risk of developing STIs that may avoid all preventative measures. Young people do not pay particular attention to the transmission of STIs to others, as well as during medical consultations, unless there is the presence of visible lesions on the genitalia and/or significant subjective symptoms. The prevention of HPV infection can be easily achieved through the use of adequate vaccination programmes. On the other hand, we currently have vaccines that confer immunity to (at most) four high-risk HPV genotypes, and we should consider that there are more than 150 genotypes of HPV and about 45 of them sexually transmissible. Thus, the take-home message should be to give an easily administered HPV vaccine to young boys and girls and reduce the risk of them developing complicated diseases. Cervix uteri cancer is most frequently diagnosed among women aged 35-44 years according to the National Cancer Institute's statistics, although new cases have also been diagnosed in women younger than 20 years. The proportion of CVC-related deaths is highest (24%) among women aged

45-54 years, while it is only 4.8% among women aged 20-34 years. No deaths have been reported for younger women.

Q: How does the practice of your colleagues in the developing world differ from your own in Europe?

A: It depends on the specific STIs and the government HPV infection/vaccination policies. All European countries are more or less involved in promoting prevention campaigns against STIs and improving the methods for HPV infection to aid early diagnosis.

Q: Aside from your own research are there any areas of reproductive health that you are particularly interested in that will be covered at ESHRE 2015?

A: Yes, the relationship between STIs and fertility, and the potential effects of electromagnetic waves (in particular mobile phones) on fertility. Many young people keep their mobile phone in the front pocket of their trousers; the long-term effects of such behaviour should be properly investigated.

Q: Has anything emerging from your current research on the effects of HPV virus in men surprised you?

A: Yes, the possible relationship with urological cancers such as BLC and PrC. We investigated HPV DNA in men who underwent surgery for non-muscle invasive BLC: 78 patients with BLC and 59 controls (affected by benign prostate hyperplasia [BPH] and candidates for surgery) were included. We found HPV DNA in about 35% of patients with BLC but in only 10% of patients with BPH. These results suggest that HPV infection can be silent in men but may play some role in the pathogenesis or the progression of different urological diseases, although this relationship should be properly investigated with large epidemiological prospective studies.

Q: What advice would you give to young physicians just starting out in a career in reproductive health?

A: New ideas represent the main resource in basic and clinical research. There are a lot of new epidemiological and observational studies with interesting results that should be properly used as a basis to promote further clinical studies. Young physicians should be involved in planning new studies on fertility and modern lifestyle in developed countries.

Q: What will be the next stage of your research into HPV virus?

A: We are now developing new research to determine the effects of HPV infection on translational mechanisms involved in PrC. Some results in terms of a relationship between HPV infection and the modification of some genes involved in the progression of PrC have already been obtained, and will be published as soon as possible.

Theo M. de Reijke

Professor of Urology, Department of Urology, Academic Medical Center (AMC), Amsterdam, the Netherlands.

Q: At what point during your medical studies did you decide to specialise in the field of urology, and what was the reason for this?

A: At an early stage during my medical studies I met a urologist and he asked me to help him with the operations and care for the patients that were operated on. Secondly, my father was diagnosed with renal cell cancer and I found that there was a lot to be investigated in this field because, besides surgery, the possibilities for treatment were minimal at that time.

Q: As a urologist with almost 30 years' clinical experience, how would you describe the pace and scale of change that has occurred in this field, and what difference has this made to patients who visit your clinic today compared with those who visited when you first started?

A: During the previous years, many developments have taken place in many fields of urology because the mechanisms of the different urological diseases are slowly being unravelled. The fact that many people are affected with urological problems also

makes urology an attractive area for industrial investment, both in terms of pharmaceuticals and technology. For the patient, this has resulted in many innovations and improvements to treatment (minimally invasive techniques, active surveillance, etc.). On the other hand, things are also more complicated for the patient because the decision to opt for one treatment or another is sometimes difficult, e.g. choosing between surgery, external beam radiation therapy (EBRT), or brachytherapy for localised prostate carcinoma.

Q: How have the innovations introduced over the past 30 years affected the training of urologists, and do you have any insight into how great the level of harmonisation is across Europe?

A: Training has become problematic, because not everyone can cover the whole field of urology anymore. Specialisation and centralisation are the 'magic words', but, if we speak about prostate cancer (PrC), then it is not only the surgical procedure that is important but also determining the correct indication for the individual patient. This means that all treatment options should be discussed and should be available. In this respect, patient-reported outcome measures are going to play a major role in the near future. Harmonisation across Europe is not very good and can vary based on the healthcare systems.

Q: You are also involved in clinical urology in Poland and Romania – what challenges are there when delivering urology services in regions typically considered resource-limited settings?

A: I was involved in introducing the urological examination in Poland at an early stage and in those early days I was amazed at how eager the residents were, the level of knowledge was also extremely good because they were highly motivated. For me, this was the driving force that convinced me to put my energy into further development. The level of urology has improved over the years and it is certainly competitive.

Q: Much of your research is focused on PrC and bladder cancer (BLC); how has the detection, treatment, and prognosis of these two conditions evolved during your time in clinical practice?

A: PrC is completely different now compared with when I started training. At that time, 60% of the patients presented with locally advanced or metastatic disease and there were no options for curative treatment. Radical prostatectomy was major surgery and only performed in very few centres in the Netherlands. The majority of patients were treated with EBRT, which cannot be compared with modern techniques. The majority of patients today present with a curative stage of the disease, and surgery has improved and is one of the standard treatments thanks to the introduction of prostate-specific antigen (PSA) testing. I remember that, at our centre, brachytherapy was re-introduced after some bad experiences in Denmark. Now, even for castration-resistant prostate cancer patients, there are many treatment options that benefit the patient.

With regard to BLC, Bacillus Calmette-Guérin (BCG) was introduced in the early 1980s and many trials have shown which patients should be treated for their non-muscle-invasive bladder cancer (NMIBC) with which agent and for how long. In MIBC, cystectomy with uretero-ileocutaneostomy, orthotopic bladder substitution, or continent diversion can be offered.

Q: Have the incidence and prevalence of prostate and bladder cancers changed during your time in practice, and are there any particular demographic groups at greater risk?

A: Many more patients with PrC are being seen due to increased awareness and the introduction of PSA testing. In BLC, smoking is the most important risk factor, and since more women started to smoke some years ago, more women are now being seen with this condition.

Q: You also participate in the development of national clinical guidelines for both prostate and bladder cancers – how frequently do the guidelines require updating and how challenging is it to arrive at a consensus with a panel of other national experts?

A: In my opinion, clinical guidelines should be living instruments and be updated on a regular basis once there are new developments. For example, the update of the PrC guideline in the Netherlands was approved in April 2014, but due to the many new

developments we have already finalised another update. Oncology should be a multidisciplinary approach, which means that many specialists are involved. If the guideline is evidence-based then there will not be much discussion, but in many areas there is no evidence from Phase III trials and in those situations consensus should be reached, which can sometimes be difficult, although that is an attractive part of the challenge.

Q: Can you give an indication of how great the level of consensus is regarding urological guidelines across Europe, and also when compared to the practice of your colleagues from other regions, such as North America, Asia, and Africa?

A: There is not much difference when comparing the guidelines around the world, it is sometimes in the details where there are some differences to be found. A guideline should, of course, be in line with local possibilities, e.g. if you state that a multi-parametric magnetic resonance imaging scan should be performed and in the whole nation there is only one scanner then you can imagine that this statement is not really clinically applicable.

Q: You recently co-authored an article describing the results from the EORTC-GU study comparing the effect of BCG with epirubicin for maintenance therapy in BLC patients of various ages – could you summarise the main findings of this important study?

A: Because in older age the immune system may be 'deprived' in some way, the idea was that BCG therapy could be less effective in older patients. In the EORTC-GU group we performed a randomised trial comparing BCG with or without isoniazid (to prevent side-effects from BCG, although it was shown that isoniazid itself induced more side-effects) and epirubicin. With a median follow-up of 9.2 years, patients >70 years of age had a shorter time-to-progression, overall survival, and NMIBC-specific survival after adjustment for EORTC risk scores in the multivariate analysis. The time to recurrence was similar compared with the younger patients. BCG was more effective than epirubicin for all four endpoints, and there was no evidence that BCG was any less effective compared with epirubicin in patients >70 years of age.

Q: The use of PSA as a biomarker of PrC in population-based screening programmes remains controversial – what is your professional opinion on the use of this biomarker for screening?

A: Population-based screening for PrC cannot be advised due to the risk of diagnosing tumours that do not need treatment. However, patients should be informed of what to expect. In high-risk groups, PSA-based testing should be used earlier and more liberally (e.g. African-Americans, those with a family history of disease, etc.).

Q: Do you know of any promising new biomarkers that may be suitable for population-based screening programmes for either prostate or bladder cancer?

A: There are many reports on markers in bladder and PrC, but these have not resulted in a real breakthrough. Perhaps the research in the USA on The Cancer Genome Atlas will help us in initiating truly individualised cancer treatment in the coming years.

Q: Could you speculate on what is likely to be the 'next big thing' in the treatment of both PrC and BLC, and how long do you imagine it will be before this will be introduced into routine clinical practice?

A: The Cancer Genome Atlas will hopefully be the breakthrough we are waiting for, because nowadays all certain stages of cancer are being treated in the same way, but each individual is different and the cancer that develops in each individual is also different, which could mean that a NMIBC should be treated in one patient with a radical cystectomy and the same tumour in the second patient could be treated with adjuvant instillation therapy.

Q: Do you have any words of wisdom for aspiring urologists aiming to specialise in the field in the future?

A: Urology is a wonderful specialisation and I have invested many hours, days, and more in this field, and the reward is great if you see what has been accomplished in the past years. No investment equals no reward. The patients deserve a doctor who is up to date. Always think about the patient and especially talk with them and treat her/him the way you would like to be treated yourself.

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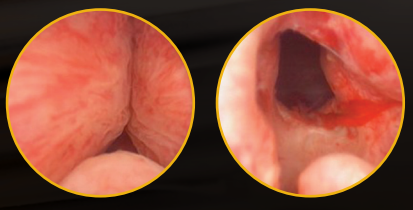

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1. Roehrborn, 2015 Urology Practice, 2-Year L.I.F.T. Study Results; 2. McVary, 2014 J Sexual Medicine; 3. Shore, 2014 Can J Urology

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This symposium took place on 21st March 2015 (18.00–19.30) as part of the Annual European Association of Urology (EAU) Congress in Madrid, Spain

Chairperson
Ian Eardley[1]
Speakers
Hartmut Porst,[2] Ignacio Moncada,[3] Béatrice Cuzin,[4] Ian Eardley[1]

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3. Hospital Sanitas La Zarzuela, Madrid, Spain
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MEETING SUMMARY

This satellite symposium was held in two sessions. The first session was offered in a traditional format where invited experts reviewed and discussed the latest concepts and developments on the management of erectile dysfunction (ED). During the second session, experts discussed clinical cases from their real-life practice in an interactive format, to facilitate discussions with the audience, and to provide participants with the most relevant aspects of ED. The symposium objectives were to review and discuss the current status of the management of ED and treatment needs for patients with ED, and to explore the latest evidence on the use of topical alprostadil cream (Vitaros®, Virirec®, Vytaros®)[1] – who benefits the most?

Opening Remarks from the Chair

Doctor Ian Eardley

In 2013 alprostadil cream received a European marketing authorisation for the treatment of ED in men from the age of 18 years.[1] In the latest updates of the European Association of Urology (EAU) guidelines on male sexual dysfunction,[2] alprostadil cream is included as a new treatment option in the management of ED. Oral selective phosphodiesterase type-5 (PDE-5) inhibitors (e.g. avanafil, sildenafil, tadalafil, or vardenafil) are recommended as the first-line pharmacotherapy, assuming that there are no contraindications or drug interactions. Other treatments and/or forms of therapy can be considered in suitable patients. In this symposium, the use of alprostadil cream as an alternative and/or first-line treatment option for patients with ED is discussed.

Management of ED: Room for Improvement?

Professor Hartmut Porst

Prof Porst discussed the treatment options for ED and what patients' expectations of treatment are in the context of an important sexual life.

The landscape of ED worldwide

According to the latest statistics published by the Durex Network Research Unit for the years 2005–2009, sex remains an important part of our lives, although the frequency of sexual activities and the importance given to these varies widely across countries.[3] The highest prevalence was observed in Greece and Brazil where up to 80–87% of the population have sex at least once a week, followed by Russia and China (72–80%), and the UK and USA (34–55%). In contrast, less than 34% of the Japanese population reported having sex once a week.[3]

The landscape for sexual disorders in men shows no significant differences worldwide. The prevalence of sexual disorders, including ED, increases with age (Table 1). In a survey conducted to evaluate the sexuality and health among older adults in the USA,[4] the prevalence of ED was estimated to be 31% in men aged 57–64 years to up to 45% in men over the age of 65 years.[4] The survey also indicated that the majority of men aged 57-85 years and suffering from sexual disorders were bothered by these, with ED at the top of the ranking (90%) followed by the lack of libido (65%), premature ejaculation, and inability to climax (65–73%).[4] 'Bothersome' was defined in the degree of 'somewhat' or 'a lot' as rated by the responders in the range of 'a lot', 'somewhat', or 'not at all'.[4]

The severity of ED also increases with age.[2-5] Over 40% of men aged 70–79 years suffer from severe ED, while over 90% of younger men aged 40–49 years have either no ED or a mild-to-moderate dysfunction.[5]

The therapeutic landscape for ED

There is a large number of treatment options ranging from PDE-5 inhibitors to intracavernosal or intraurethral alprostadil (prostaglandin E_1 [PGE_1]), vacuum erection devices, hormone replacement therapy (testosterone), sexual counselling, and penile implants. The mode of action differs between therapeutic modalities (Figure 1). PDE-5 inhibitors block the cleavage of cyclic guanosine monophosphate (cGMP) via inhibition of the enzyme PDE-5.[6,7] Instead, alprostadil activates the cyclic adenosine monophosphate (cAMP) pathway. Alprostadil binds directly to the G-protein-coupled PGE_1 receptors on the smooth muscle cell surface, to convert adenosine triphosphate to cAMP. An enzyme cascade ultimately results in a reduction in the cytoplasmic Ca^{2+} available for smooth muscle contraction.[8] The intracavernous accumulation of cGMP or cAMP causes relaxation of the cavernous arteries and smooth muscle cells lining the blood vessels of the penis, ultimately resulting in an increase of arterial blood flow with enlargement of the cavernous bodies. This process impedes return of the venous blood and maintains erection.[6,7,9]

Table 1: Prevalence (%) of sexual disorders by age in adults in the USA.[4]

Age, years	Sexual disorder*		
	Premature ejaculation	Delayed/absent ejaculation/orgasm	ED
57–64	29.5 (23.4–35.7)	16.2 (11.9–20.5)	30.7 (25.3–36.0)
65–74	28.1 (23.4–32.9)	22.7 (17.5–27.9)	44.6 (38.7–50.5)
75–85	21.3 (13.2–29.3)	33.2 (25.0–41.5)	43.5 (34.5–52.4)

*Values represent prevalence % estimates (95% confidence intervals)
ED: erectile dysfunction.

Prescribing information can be found at the end of the article.

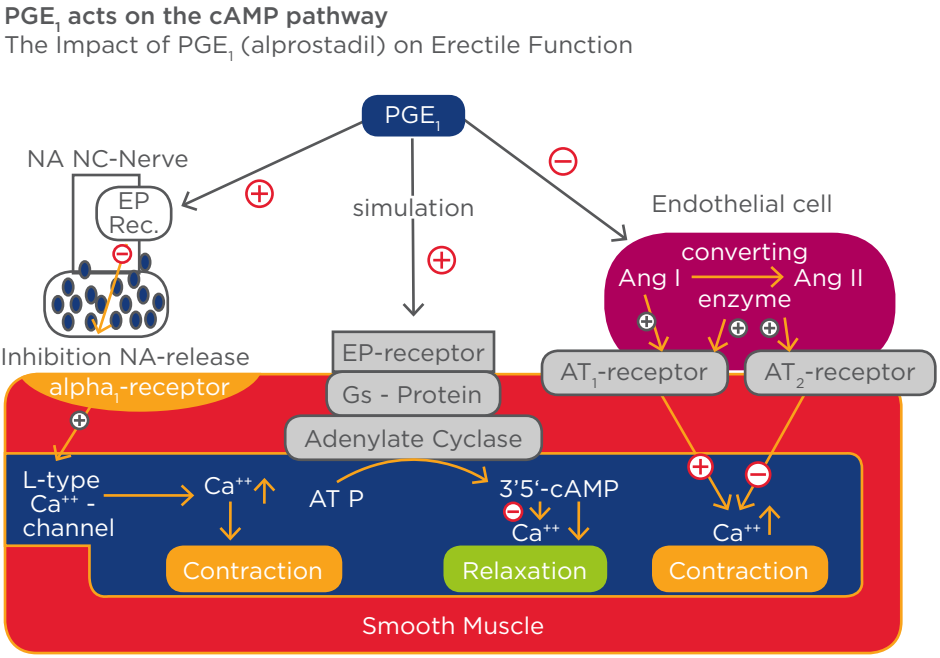

Figure 1: Mode of action of alprostadil (PGE_1) versus PDE-5 inhibitors.
cAMP: cyclic adenosine monophosphate; PGE_1: prostaglandin E_1; PDE-5: phosphodiesterase type-5; ATP: adenosine triphosphate.
Adapted from Porst[6,7]

When seeking help, patients demand treatments that are highly effective (i.e. rigid erection and reliable), easy to use (i.e. rapid onset and reasonable duration of action, with no interference with food and alcohol), with an optimal tolerability and at affordable cost.[10] The importance of having a drug that meets the spontaneous aspect of sexual activity, therefore not requiring advance anticipation, was shown in a study by Fisher et al.;[11] the majority of the couples (two-thirds) engage in sexual activity in a timing and pattern manner that is unpredictable, and only a low proportion (4–5%) usually anticipate their sexual activity.[11] Some factors may limit the use of systemic administration of PDE-5 inhibitors. Except for tadalafil, the rate and extent of absorption of PDE-5 inhibitors (avanafil, sildenafil, and vardenafil) is reduced substantially after a meal. PDE-5 inhibitors show decreases of up to 39% in the peak in plasma concentration (C_{max}) and delays of 1.0–1.25 h in the mean time to the maximum concentration compared with their administration in the fasted state.[12–14]

PDE-5 inhibitors are the first-line on-demand therapy (Level 1a and 1b evidence) for ED.[2] Overall Sexual Encounter Profile (SEP)-3 (SEP question 3 – measure of erectile function [EF] maintenance: 'Did your erection last long enough for you to have successful intercourse?') success rates range between 60% and 75% in mixed ED populations, but decrease below 50% in special difficult-to-treat populations (e.g. cardiovascular disease [CVD], diabetes, radical prostatectomy [RP], hypertension, failure of PDE-5 inhibitor treatment).[2] In patients who have undergone RP, the damage to the autonomic nerve supply to the penis makes PDE-5 inhibitor therapy ineffective.[15] In this group of patients, SEP-3 success rates of 34% and 41%, following treatment with vardenafil or tadalafil (20 mg), respectively, have been reported.[16,17] Similarly, the lowest responses to sildenafil have been reported in patients after RP, although some variation exists between difficult-to-treat patient subgroups.[15]

Compliance with PDE-5 inhibitor treatment has been shown to decrease over time. In a mean follow-up of 1–3 years, overall up to 49% of responders to sildenafil, vardenafil, and tadalafil reported that they had discontinued their treatment.[18,19] Common reasons for discontinuation were effect below expectations, high cost, loss of interest in sex, and inconvenience of obtaining sildenafil.[18,19] Non-effectiveness was the leading reason for discontinuation of sildenafil treatment.[20]

The adverse event (AE) profiles of PDE-5 inhibitors are generally similar. Common systemic AEs include headache (5–15%), flushing (3–14%), dyspepsia (up to 10%), and nasal congestion (2–9%).[21–24]

In summary, there is no ED therapy that can serve all patients effectively and satisfyingly. Even with PDE-5 inhibitors, drop-out rates of >50% are observed – common determinant factors are lack of efficacy, in particular lack of full rigidity and non-tolerable systemic AEs. Because PDE-5 inhibitors are not as effective in patients who have undergone RP or are diabetic, a substantial unmet medical need exists among patients who have ED as a result of these conditions. As highlighted by Prof Porst, all of this evidence indicates that 'there is still room for improvement in the management of ED'.

The First ED Topical Treatment: A New Paradigm?

Professor Ignacio Moncada

Prof Moncada's presentation focussed on the value of topical alprostadil as a new treatment option for patients with ED.

A new topical formulation of alprostadil – mechanism of action

Topical alprostadil cream delivers the efficacy of alprostadil in an 'easy-to-use' formulation that does not involve systemic administration. The vasodilator alprostadil is a synthetic analogue of PGE_1 – equivalent to the naturally occurring PGE_1. Alprostadil cream is formulated in combination with a novel skin permeation enhancer, dodecyl-2-N, N-dimethylamino propionate, which allows rapid and complete absorption of alprostadil through the skin cells (Figure 2).[8,9,25] Alprostadil produces corporal smooth muscle relaxation by the activation of adenylate cyclase and subsequent accumulation of cAMP that in turn results in erection; this mechanism is independent of the nitric oxide–cGMP mechanism.[8,26]

EF is normal after application of alprostadil cream based on haemodynamic parameters (mean peak and end of systolic velocity and mean resistance index measured with Duplex ultrasonography) to those observed with intracavernosal alprostadil injection.[26] Alprostadil cream allows on-demand treatment of ED that only requires a simple and non-invasive method of application.[25]

Clinical significance of alprostadil cream – efficacy and safety profile

The efficacy and safety of alprostadil cream has been demonstrated in Phase II and III clinical trials.[27–29] Results from two multicentre, placebo-controlled, Phase II studies have demonstrated significant improvements in EF based on the change in EF score from baseline to final visit after 6 weeks of treatment with alprostadil cream, in men with mild-to-moderate (n=161) or severe (n=142) ED.[27] Clinically relevant changes from baseline in the International Index of Erectile Function (IIEF-EF) and local EF domain scores were observed for the highest dose (300 µg) in patients with severe ED. Efficacy measures of the ability to achieve erection (change in score relative to baseline for question 3), ability to maintain erection after penetration (change in score relative to baseline for question 4 ['When you attempted sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?']), vaginal penetration success rate (SEP), and patient self-assessment of erection scores were also improved with alprostadil cream.[27] The proportion of patients reporting an improvement in erections, as assessed by the global assessment questionnaire (GAQ: 'While using the study medication, did you feel your erections improved?'), was significantly higher ($p<0.001$) in patients with severe ED treated with alprostadil cream (83% [n=35]) with 300 µg versus placebo (26% [n=35]). Most reported AEs (65% local AE plus 3% systemic AE) were mild or moderate, transient, and localised.[27] In results from a study conducted with pooled data from these two Phase II studies (n=303), alprostadil cream demonstrated increased efficacy versus placebo in a dose-dependent manner (50–300 µg).[26,27]

The efficacy and tolerability of alprostadil cream was confirmed in two Phase III randomised controlled trials conducted in men with moderate-to-severe ED (mean IIEF-EF score: 13.6).[28,29] The first study (n=1,732) included patients with a mean age of 60 years (37% aged >65 years) with a wide range of concomitant comorbidities (diabetes [22%], CVD [32%], prostatectomy [12%], hypertension [48%]) treatments (nitrates or alpha-blockers [16%]), and patients who had previously failed to respond to sildenafil (19%).[28] After 12 weeks of treatment, alprostadil cream 300 µg significantly improved EF and intercourse ability compared with placebo. As observed in

Phase II studies, significant improvements in all efficacy parameters (IIEF-EF, SEP-2, and SEP-3) were observed with alprostadil cream compared with placebo.[28] The majority of the successful attempts took place during the first 30 mins following application of alprostadil cream 300 µg.

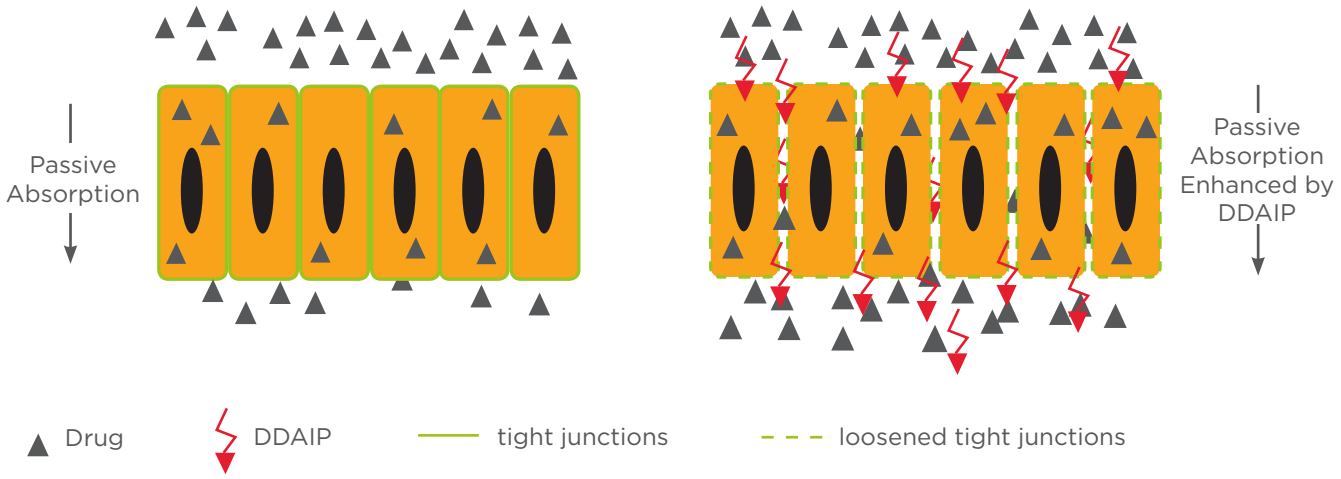

Figure 2: Permeation enhancer dodecyl-2-N,N-dimethylamino propionate (DDAIP) – mechanism of action.
Adapted from Moncada, Cuzin[9]

Table 2: Common adverse effects (AEs) for alprostadil cream 300 µg – results from clinical trials.[9,28]

	Placebo (n=434)	Alprostadil topical cream 300 µg (n=434)
Systemic AEs		
Patient, n (%)		
Overall	3 (0.6)	13 (0.3)
Nervous system	1 (0.2)	11 (1.2)
Dizziness	1 (0.2)	5 (0.5)
Headache	1 (0.2)	N/A
Hyperaesthesia	0 (0)	6
Skin and appendages	1 (0.2)	2 (0.5)
Rash	1 (0.2)	2 (0.5)
Local AEs		
Patient, n (%)		
Overall	51 (0.6)	279 (64.9)
Genital pain	2 (0.5)	76 (17.5)
Penile burning	26 (0.6)	100 (23)
Penile erythema	9 (2.1)	49 (11.3)
Partner, n (%)		
Overall	13 (3)	28 (6.5)
Vaginal burning	8 (1.8)	19 (4.4)
Vaginitis	5 (1.2)	9 (2.1)

As observed in Phase II studies, the majority of AEs were mild-to-moderate, transient, and localised. The long-term (up to 9 months) efficacy and safety profile of alprostadil cream has also been demonstrated in an open-label study conducted with 1,161 patients (mean age 60 years) with mild-to-severe ED (IIEF-EF score ≤25).[29] Most of these patients had participated in the Phase III trials. The majority of the patients (93%) had a mean ED duration of ≥12 months. Patients were initially administered with alprostadil cream 200 µg that could be titrated up or down to 300 µg or 100 µg for up to 9 months (two doses/week). Significant improvements based on the change from baseline in IIEF-EF score were observed after 6 months of treatment (n=119) with alprostadil cream 300 µg (score of 21) compared with placebo (score of 11).[29] As observed in Phase II and III studies, adjustment to 300 µg alprostadil facilitated the greatest improvement in EF, based on SEP-2 and SEP-3 responses.[29]

No major differences compared with placebo have been observed in terms of systemic AEs – as expected from a drug with a local site action.[9,28] The incidence of local AEs, however, was higher among patients treated with alprostadil (65%) compared with placebo (10%) (Table 2).[9,28] All local AEs were mild or moderate and of short duration. In the long term, the incidence of AEs decreased overall (34%).[29]

Results from the clinical studies demonstrate that alprostadil cream can be considered as a valid therapeutic option in patients with ED. Patients who may benefit the most include treatment-naïve patients, patients who do not respond, cannot tolerate, or do not accept PDE-5 inhibitor therapy, and patients treated with nitrates.[25,26,29]

Results of a survey of patients (n=152) asked to express their preferences for an ED treatment according to the route of administration (systemic/oral, injectable, intra-urethral, or cream/topical) showed that 53% of subjects would select a cream as the first choice.[9] In summary, alprostadil is offered in a new formulation, a cream that combines it with a novel skin-permeation-enhancing drug-delivery system. The new topical formulation allows fast onset of action, with reliable efficacy and no anticipated interference with other drugs, food, or alcohol consumption. It is easy to use, well suited for a broad range of patients (e.g. undergoing other therapies) and, more importantly, with low incidence of unexpected systemic AEs.

Alprostadil Cream: Patients Who Could Benefit Most

Doctor Béatrice Cuzin

Dr Cuzin reflected on the population of patients with ED who could benefit the most from treatment with alprostadil cream. As already discussed during the symposium, the efficacy and safety of alprostadil cream has been demonstrated in clinical studies conducted in large study populations.[9,28,29] The studies involved patients across a wide spectrum of disease severity and concomitant conditions and/or treatments. Clinical populations studied included patients who were not candidates for treatment with PDE-5 inhibitors (non-responder, contraindicated), severe ED patients, and difficult-to-treat patients (i.e. failed previous PDE-5 inhibitor therapy [specifically sildenafil], with stable CVD, hypertension, diabetes, those who had undergone prostatectomy, and those aged >65 years). Clinical response was evaluated according to medical history and severity of ED.[9,28,29]

Of special consideration is the interpretation of instruments used to measure patient-reported outcomes recommended by the USA's FDA guidelines and emerging methods.[30] There is a need to provide evidence on outcomes based on qualitative (collecting input directly from patients and clinical experts) and quantitative (use of a particular responder threshold as an indicator of meaningful change from the patient's perspective) methods that can help to draw conclusions about the statistical significance and clinical relevance of the treatment. To evaluate treatment-related changes in terms of clinically relevant improvement it is therefore an essential aspect towards understanding treatment efficacy, interpreting the results across studies, and managing patients effectively.

A new paradigm for patients who are not satisfied with, cannot tolerate, or do not accept PDE-5 inhibitor therapy or other ED treatments

A new treatment for ED can be offered to these patients that could help address their unmet needs with other treatments. Current therapy with ED, usually consisting of systemic treatment with PDE-5 inhibitors, does not always reflect a patient's preference. Patients demand easy-to-use treatments with a rapid onset of action and no interference with food and/or alcohol.[9,10] Acceptable AEs are an important consideration at

the time of selecting treatment for ED. In a study conducted to evaluate the efficacy and safety of alprostadil formulated for intracavernosal treatment, penile pain was very commonly reported (50%), followed by haematoma or ecchymosis (8%) and prolonged erections (5%).[31] The incidence of systemic treatment-related AEs is high with PDE-5 inhibitors. Common AEs include headache (13–16%), flushing and dyspepsia (4–12%), back pain (7%), and myalgia (6%).[2]

Table 3: Two case studies.

Clinical history and examination	Points of discussion	Outcome
Case 1		
• 56-year-old • ED for the past 12 months (difficulty to maintain erections) • Appendectomy (40 years old) • Hypertension for 7 years (bisoprolol) • Ex-smoker • BMI 27 kg/m^2, waist circumference 99 cm, BP 125/80 (under β-blockers), HR 72/min, BPH symptoms, normal genitalia	• Heterosexual, with an intermittent sexual relationship with the same partner (past 18 months) • No history of oral PDE-5 use • IIEF-EF score=15 – moderate ED • Normal FBC and U&E: not diabetic (only possible impaired glucose intolerance), normal levels of cholesterol, testosterone, and PSA • Potential risk of CVD (overweight, hypertension) – systemic treatment could be indicated as first-line • Afraid of the risk of CVD associated with the use of PDE-5 • Unwilling to let the partner take part in the discussion for treatment choices	• Patient opted for topical alprostadil cream 300 µg • Successful outcome with an EF domain score of 27 when using the cream
Case 2		
• Localised prostate cancer diagnosed 12 months earlier • Preoperative PSA 5.4 ng/ml • Robotic RP (bilateral nerve sparing) • Pathology showed T2 Gleason 4+3 adenocarcinoma, negative margins • Married for 35 years (60-year-old wife) • Tadalafil 5 mg/day (from Week 3 after surgery) • No spontaneous or nocturnal erections, even with additional on-demand PDE-5 therapy • IIEF-EF domain score 10	• Had an effective trial dose of intracavernous alprostadil 10 µg, but caused severe pain – unwilling to continue with injections	• Topical alprostadil, cream was used with good efficacy and no major adverse effects

BMI: body mass index; BP: blood pressure; BPH: benign prostatic hyperplasia; CVD: cardiovascular disease; ED: erectile dysfunction; EF: erectile function; FBC: full blood count; HR: heart rate; IIEF-EF: International Index of Erectile Function; MUSE: medicated urethral system for erections; PDE-5: phosphodiesterase type-5; PSA: prostate specific antigen; RP: radical prostatectomy; U&E: urea and electrolytes.

In contrast, common local AEs with alprostadil cream include penile burning sensation (25%) and penile erythema (11%).[25] Furthermore, AEs leading to discontinuation were rarely reported with alprostadil cream – 4.3% reported in clinical trials[29] compared to 12% with PDE-5 inhibitors[19] and >40% with PGE1 intracavernous injections.[2]

Difficult-to-treat patients (diabetes, cardiovascular disease, prostatectomy, hypertension)

Patients with severe ED and comorbidities are of particular concern. Treatment with alprostadil cream significantly improves EF in patients with severe disease in a dose-dependent manner (measured by IIEF-EF, SEP-2, and SEP-3). The proportion of patients in the Phase II study reporting significant improvements in the GAQ score was up to 76% (200 µg) (n=35) and 83% (300 µg) (n=35) compared with 26% in the placebo group (n=35).[27] In a post-hoc analysis of the Phase III studies, clinically significant changes in the IIEF-EF scores were demonstrated across subgroups of patients with different comorbidities (diabetes, CVD, prostatectomy, hypertension) using 300 µg alprostadil regardless of the ED severity.[30]

In summary, topical alprostadil cream has been demonstrated in clinical trials to be effective and well tolerated in the treatment of ED, across a wide spectrum of patients and severities of ED.

In patients with concomitant conditions such as diabetes, hypertension, CVD, or in those who have undergone prostatectomy, treatment with alprostadil cream resulted in significant improvement in EF, reaching the normal range of IIEF-EF, defined as ≥26 score for some patients.[9] The results indicate that alprostadil cream is a valid alternative option for any type of patient with ED. Patients with a history of CVD, sildenafil failure, or prostatectomy treated with alprostadil cream 300 µg show consistent statistically significant improvements in vaginal penetration and EF maintenance.

Following its marketing authorisation by the European Health Authorities in 2013, topical alprostadil has been approved in more than ten countries. Alprostadil cream is the first innovative ED product in nearly a decade, and has the potential to help a large number of patients, including treatment-naïve patients; patients preferring a local treatment for a local problem; patients unable to tolerate or who do not accept PDE-5 inhibitor therapy or other ED treatments; patients over the age of 65 years; difficult-to-treat patients (i.e. diabetes, CVD, prostatectomy, hypertension, PDE-5 failure); patients with CV risk and with CV comorbidities treated with nitrates (except if having strong contraindications for sexual activities); and patients with benign prostatic hypertrophy treated with α-blockers.[9,25]

Clinical Cases: Discussion With the Experts

Doctor Ian Eardley

During the second session of the symposium, the panellists evaluated two clinical cases from their clinical practice. Following a detailed description of each real-world situation by Dr Ian Eardley, panellists had the opportunity to look in depth at each case in order to make decisions about the most appropriate treatment options (Table 3).

Concluding Remarks

Topical alprostadil cream is a valid treatment option for patients affected with ED and can be considered a first-line choice for a wide range of patients. This new formulation of alprostadil combined with a novel skin permeation enhancer allows a local and fast onset of action with reliable efficacy, while maintaining patient acceptability in the long term.

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NAVIGATING THE mCRPC LANDSCAPE: EXPLORING KEY CLINICAL DECISION POINTS

Summary of presentations from the Bayer-supported satellite symposium, held at the European Association of Urology (EAU) Congress, Madrid, Spain on 22nd March 2015

Chairperson

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Speakers

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MEETING SUMMARY

The Bayer satellite symposium was introduced by Prof Fred Saad, who gave an introduction into the use of radium-223 in metastatic castration-resistant prostate cancer (mCRPC). Results from the recent Phase III ALpharadin in SYMptomatic Prostate Cancer (ALSYMPCA) study were also presented. Profs Kramer, Tombal, and Gschwend then each presented case studies on patients they had treated with radium-223. Each speaker also provided their own personal view and recommendations for use of radium-223 based on their experience with these patients. Prof Gschwend concluded the symposium with important considerations for the urologist in using radium-223 in mCRPC.

Investigating Clinical Practice With Radium-223 Dichloride in Metastatic Castration-Resistant Prostate Cancer to Optimise Patient Outcomes

Professor Fred Saad

The past 5 years have seen the emergence of several therapies for metastatic castration-resistant prostate cancer (mCRPC). Prior to 2010, androgen deprivation therapy (ADT) was the main treatment for non-metastatic disease while docetaxel was used in the metastatic castration-resistant setting.[1] Currently, multiple treatment options exist that can be used both in the chemo-naïve and post-chemotherapy settings. The availability of several therapies has improved our outlook on the outcome of mCRPC.

The bone is the most common site for metastasis in prostate cancer (PrC) patients.[2] Bone metastases are a significant cause of morbidity and

mortality and can significantly increase the risk of skeletal-related events (SREs) such as fractures.[2,3] In fact, SREs are associated with increased mortality in mCRPC patients with <1% experiencing a 5-year survival rate.[4] Radium-223 dichloride is the first alpha-emitting radionuclide that selectively binds to areas of increased bone turnover in bone metastases.[5,6] Being a calcium mimetic, radium-223 is able to be incorporated into newly formed bone material. The short range of the alpha particles means that toxic effects on adjacent healthy tissue and bone marrow are minimal, thus giving radium-223 a favourable safety profile.[5-7]

The ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) study was a Phase III clinical trial that evaluated the effects of radium-223 on survival in mCRPC patients.[8] A total of 921 patients were randomised 2:1 to either radium-223 or placebo plus best standard of care. Radium-223 was administered as six injections at 4-week intervals. Patients were eligible to participate in the study if they had histologically confirmed progressive mCRPC with two or more bone metastases and no known visceral metastases. The primary endpoint was overall survival (OS). As many as 40% of patients had not received prior treatment with docetaxel, which enabled investigators to understand the effects of radium-223 in the chemo-naïve setting.[8]

The results of the study showed that median OS was improved in the radium-223 group compared to the placebo group (14.9 versus 11.3 months; hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.58—0.83; p<0.001).[8] The results demonstrated a 30% reduction in the risk of death with radium-223 compared to placebo. Radium-223 was shown to improve all secondary endpoints significantly in comparison to placebo; it significantly prolonged both the median time to first symptomatic skeletal event (SSE) (15.6 versus 9.8 months; HR: 0.66; 95% CI: 0.52—0.83; p<0.001) and median time to prostate specific antigen (PSA) progression (3.6 versus 3.4 months; HR: 0.64; 95% CI: 0.54—0.77; p<0.001). Importantly, radium-223 was also able to delay the median time to increase in total alkaline phosphatase level (ALP) (7.4 versus 3.8 months; HR: 0.17; 95% CI: 0.13—0.22; p<0.001). Furthermore, a higher proportion of patients in the radium-223 group demonstrated a ≥30% reduction in ALP as well as normalisation at this level (p<0.001 in each case).[8]

Quality of life (QoL), as measured by the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire, was also shown to be significantly improved in radium-223-treated patients.[8] Radium-223 also demonstrated a favourable safety profile, where the overall incidence of adverse events (AEs) was similar between the radium-223 and placebo groups.[8] Additionally, no clinically meaningful differences in the frequency of haematological AEs in patients receiving chemotherapy after radium-223 were observed between the study groups.[9] The strong efficacy and safety profile of radium-223 has led to its recommendation as a Grade A or Category 1 therapy for mCRPC in recent national and international guidelines.[1,10-13] Since initiation of the ALSYMPCA trial, additional PrC therapies have emerged onto the market, offering mCRPC patients multiple treatment options. Further research aims to find optimal combinations and sequences of existing therapies as well as tailoring treatment for individual patients.

Key Points

- The bone is a common site for metastases in PrC patients.
- Radium-223 is a novel agent shown to extend OS by targeting bone metastases in patients with mCRPC.
- The Phase III ALSYMPCA study showed that radium-223:
  - improved OS in mCRPC patients
  - caused a 30% reduction in the risk of death
  - improved the time to first SSE and time to PSA progression
  - has a favourable safety profile
- Radium-223 is recommended as a Grade A or Category 1 therapy for mCRPC in national and international guidelines.

Steering a Course in the Pre-Chemotherapy Setting: Insights From the Clinic and Patient Case Studies

Professor Gero Kramer

Results from the ALSYMPCA trial have shown that radium-223 has an OS benefit within the range of existing mCRPC treatments.[8,14-18] Radium-223 can be used in different disease settings including mildly symptomatic mCRPC as well as pre and post-chemotherapy. The case of a 64-year-old

patient diagnosed with mCRPC in 2009 was presented. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, Gleason score 7 (4+3), and PSA 14 ng/ml. Upon diagnosis, the patient opted for alternative treatment consisting of thermo-immune therapy plus short-term ADT. In February 2012 the patient exhibited a tumour stage of pT3b pN1 M0, Gleason score 9 (4+5), PSA 7 ng/ml, and ultimately underwent radical prostatectomy. Four months later the patient presented with multiple bone metastases on the lumbar spine, thoracic spine, and ribs, and commenced treatment with degarelix and denosumab.

Following treatment, PSA decreased from 33 to 0.5 ng/ml but eventually progressed again despite therapy with bicalutamide. The patient started treatment with abiraterone but eventually had to stop this owing to PSA and radiographic progression. PSA levels were 290 ng/ml and a bone scan showed multiple bone metastases in the spine, bony pelvis, ribs, and femur. There were no lymph node or visceral metastases. The patient had mild pain (visual analogue scale [VAS] 2) in the lumbar spine but took no pain medication.

Prof Gschwend agreed that either option of radium-223 or chemotherapy was reasonable. Prof Tombal chose to treat with radium-223 as the patient had no visceral metastases and treating with radium-223 still gave the patient the option of having chemotherapy later. Prof Tombal went on to explain the importance of discussing treatment options with the patient and predicted that if patients know they have an alternative to chemotherapy then they are likely to opt for radium-223. However, it is important to bear in mind that patients with an ECOG performance status of 2 are unlikely to benefit from radium-223 treatment as their survival expectancy is <1 year. Prof Saad chose treatment with docetaxel due to the patient's quick progression as indicated by his PSA levels. Prof Kramer also opted for docetaxel and confirmed that this was the option presented to the patient.

However, the patient refused treatment with docetaxel and commenced radium-223 treatment instead. After two cycles of radium-223 treatment, PSA levels had still progressed from 879 to 1,009 ng/ml with ALP stable at 110 U/l. The patient had no visceral metastases. All speakers agreed that continuation with radium-223 would be the best option and Prof Kramer confirmed that this was the course of treatment chosen for the patient. Upon treatment with radium-223, the patient experienced an initial flare in PSA levels, however PSA eventually declined after the third cycle of treatment until the sixth cycle to a level of 524 ng/ml. ALP and bone alkaline phosphatase remained stable throughout the treatment period. After two cycles of radium-223 pains disappeared completely. Interestingly, prostate-specific membrane antigen positron emission tomography magnetic resonance imaging (PSMA PET MRI) did reveal an increase in activation of PSMA expression. Computerised tomography (CT) scans confirmed stable disease with no new metastases after six cycles of treatment and the patient did not suffer any side-effects.

In summary, this case study showed that radium-223 was well tolerated and that commencing treatment with radium-223 as soon as symptoms appear is appropriate. It also appears that radium-223 can be used in chemo-naïve patients with no visceral metastases. Although CT scans cannot be used to determine when to terminate radium-223 treatment, they should be done at intervals to monitor metastases. Multiple treatment options for mCRPC now exist and the best course of treatment should be determined by the individual patient profile, clinical symptoms, and patient preference.

Key Points

- Radium-223 can be used across the range of symptomatic mCRPC settings, e.g. pre or post-chemotherapy.
- Radium-223 may be considered in patients as soon as their bone metastases become symptomatic.
- Choice of treatment should be determined by the individual patient profile, clinical features, and patient preference.

Current Approaches in Monitoring mCRPC Treatment: Guiding Examples From Real-Life Patient Case Studies

Professor Bertrand Tombal

A patient case was presented of a 75-year-old man with ECOG performance status 0, Gleason score 7, and PSA 75 ng/ml. No metastases were observed and the patient was started on external beam radiation therapy plus degarelix. After 1 year

of hormonal therapy the patient experienced PSA progression and reported a pain score of 2/10 on the Brief Pain Inventory-Short Form (BPI-SF) questionnaire. A discussion ensued among the speakers as to the best course of therapy for this patient; treatment with docetaxel or abiraterone were considered the most suitable options. The current European Association of Urology (EAU) guidelines do not provide a clear-cut recommendation for the most effective drug for secondary treatment,[19] thus leaving the physician to decide the best course of treatment. Unlike abiraterone, enzalutamide, and radium-223, docetaxel does not have stringent criteria for use and can be used in patients with visceral metastases, small-cell PrC, and those taking analgesics.[8,15,17,20,21] The ability of docetaxel to be used in multiple disease states means that it is a widely used therapy for secondary treatment of mCRPC.

The two main treatment goals in mCRPC are prolonging OS and prolonging symptom-free survival. As many as 91% of mCRPC patients experience bone metastases, leading to SREs and SSEs which are often painful, thus reducing QoL.[20,21] Bone-targeted therapies, such as zoledronic acid and denosumab, have demonstrated a delay in the time to first SRE and decreased the total number of SREs during the lifetime of the patient.[22,23] Additionally, radium-223 has been shown both to decrease the incidence of SSEs as well as to prolong OS regardless of bisphosphonate use.[24]

This patient was a good candidate for treatment with radium-223 as he had bone metastases but no visceral metastases, and he had pain with radiological progression on abiraterone and experienced a moderate deterioration in ECOG performance status. After five injections of radium-223 an overall improvement was observed; ALP levels stabilised, pain decreased, and the patient reported an improved health status as measured by the EuroQOL five dimensions (EQ-5D) questionnaire. Continuing treatment of the patient will focus on maintenance therapy.

Radium-223 also offers several advantages as a therapy for mCRPC; it is a standard injectable and therefore straightforward to use, the patient can be released immediately following treatment, and the patient needs only to observe standard hygiene measures and does not need to undergo sterilisation. Contamination and accidental intake are unlikely, and exposure to other persons is negligible. In case of emergency surgery or security issues, patients carry a patient card stating that they have been treated with a radionuclide. In terms of practical considerations it is important for the urologist to decide on the choice of treatment in conjunction with the nuclear medicine physician. Once initiated, six cycles of radium-223 should be administered unless clinical deterioration or visceral metastases are observed. As there is no single marker to measure efficacy, it is recommended that both PSA and ALP are used alongside a pain scale such as the BPI-SF. It is also important to evaluate the health status of the patient by using a patient questionnaire such as the EQ-5D. Patient follow-up should be conducted every 3 months by a urologist or specialist nurse with monthly blood tests carried out to monitor toxicity.

Key Points

- The EAU guidelines do not provide a clear recommendation of therapy for secondary treatment of mCRPC, leaving physicians to decide on the best course of treatment.
- Patients with bone metastases but no visceral metastases are good candidates for radium-223 treatment.
- Patients should undergo six cycles of radium-223 unless clinical deterioration is observed.
- Radium-223 not only prolongs OS but also delays symptomatic skeletal events.

Outlook of the Changing mCRPC Treatment Landscape: Learning From Real-Life Experiences

Professor Jürgen Gschwend

Radium-223's favourable safety profile and unique mode of action means that it has potential to combine with novel anti-hormonal agents to treat mCRPC. Abiraterone potently blocks androgen biosynthesis and is also an inhibitor of CYP17, a key enzyme responsible for testosterone synthesis.[25] Enzalutamide works by blocking the binding of dihydrotestosterone to the androgen receptor, it also inhibits the nuclear translocation of androgen receptor and binding to DNA.[26]

Two patient case studies were presented in which radium-223 had been used in combination with other agents. The first case study presented was that of an 81-year-old man with newly diagnosed

metastatic PrC in July 2010. The patient had pelvic bone metastases, Gleason score 9 (4+5), PSA 54.5 ng/ml, ALP 230 U/l, and an ECOG performance status 0. The patient experienced no pain and was treated with complete androgen blockade for 30 months, which resulted in a decline in PSA. Following a diagnosis of mCRPC, denosumab therapy was initiated, however PSA progressed to 36.4 ng/ml. Therapy with bicalutamide was terminated and single androgen ablation therapy was maintained. The patient experienced another PSA rise to almost 50 ng/ml, ALP 220 U/l, and mild bone pain; in addition, small retroperitoneal lymph nodes (RLNs) were detected but no bone metastases.

In April 2013 the patient commenced treatment with abiraterone and prednisone. Although a rapid decline in PSA levels was observed, abiraterone treatment had to be terminated owing to peripheral oedema and cardiac insufficiency. However, due to progressing PSA levels, the patient started treatment with enzalutamide. After 10 months of abiraterone treatment and 1 month of enzalutamide, bone metastases were detected, small stable RLNs were present, and there was moderate bone pain, increasing PSA, and ALP 220 U/l. It was then decided to initiate treatment with radium-223. After six cycles of radium-223, PSA declined from 7.9 to 1.8 ng/ml. ALP also decreased towards more normal values. The patient also experienced an improvement in pain (maximum 2/10 VAS). Bone scans showed a decreased bone turnover and PSMA PET scans showed decreased PSMA uptake in the bone lesions.There was also no change in lymph node metastases. The patient had a good performance status (ECOG 0) and overall the treatment was well tolerated with no relevant side-effects.

The second case study described a 71-year-old patient who was diagnosed with bone prostatic hyperplasia and subsequently underwent a transurethral resection of the prostate. He was later diagnosed with PrC (Gleason score 6 [3+3]) and received bicalutamide treatment due to rising PSA (11.3 ng/ml). Despite this, the patient developed bone metastases in the spine and pelvis and was later treated with luteinising hormone-releasing hormone (LHRH) analogue and eventually also received palliative radiation due to bone pain.

After 19 months of receiving LHRH analogue, the patient was experiencing increasing pain (3/10 VAS) and a CT scan showed only small lymph node metastasis. The patient then commenced treatment with radium-223. After four cycles ALP levels declined; however, PSA levels increased from 58.1 ng/ml at the start of radium-223 treatment to 127.8 ng/ml. Pain levels decreased from 4/10 to 2/10 VAS. Due to concerns with the increasing PSA level, the patient initiated treatment with abiraterone and prednisone in addition to radium-223. This resulted in a rapid decline in PSA to 38.3 ng/ml with stable ALP. Clear remission was also observed in bone scans conducted after undergoing three cycles of radium-223.

Both of these cases demonstrate that radium-223 can be combined with abiraterone or enzalutamide and that this combination is well tolerated. However, further investigation in clinical studies is required. Importantly, PSA is not the main marker for response to radium-223; therefore, PSA decline should not be expected in every case. Treatment decisions should not only be based on PSA but should also take into account ALP, clinical features, level of pain, performance status, and patient wellbeing.

There are several ongoing studies investigating the effects of radium-223 in mCRPC. These include a Phase III study in combination with abiraterone and a Phase II study in combination with abiraterone and enzalutamide.[27,28] The effects of radium-223 in other solid tumour types (e.g. breast) are also being investigated.

Key Points

- The combination of radium-223 with novel antihormonal agents, namely abiraterone and enzalutamide, for the treatment of mCRPC appears efficacious and well tolerated, although prospective data will be needed to confirm this.
- There is no single robust marker for assessing treatment response to radium-223.
- Physicians should not expect to see a PSA response with radium-223. Impact on other traditional markers of treatment response (pain, ALP, radiographic progression) are mixed. Treatment with radium-223 should be continued through six cycles unless clear clinical progression or severe side-effects occur.
- Several clinical trials are further evaluating the effects of radium-223 in PrC and other solid tumours.

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IS THE YOUNG PATIENT A CANDIDATE FOR ACTIVE SURVEILLANCE?

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Avoid prostate-specific antigen tests where there is little to gain

Prostate-specific antigen (PSA)-based screening has been shown to reduce prostate cancer (PrC) mortality. Evidence for this reduction comes from the European Randomized Study for Screening of Prostate Cancer (ERSPC), which is considered to be the most important and powerful screening study conducted in this field. In the ERSPC, mortality due to PrC was reduced by 27% in screening attendees. On the other hand, PSA-based screening is associated with overdiagnosis and overtreatment of local disease. However, this phenomenon is seen in every kind of disease screening programme (breast cancer, colon cancer, coronary heart disease, etc.). In PrC screening, the rate of overdiagnosis ranges around approximately 50%, which makes other screening treatment strategies, such as active surveillance (AS), necessary. Importantly, the autoptic prevalence of microfocal disease in men aged 40-59 years is as high as 25%, but only 8% of these men will suffer from PrC during their lifetime.

Thus, the first step is to avoid screening in men where there is little to gain

Retrospective data from the Malmö Preventive Project have shown that PSA is an excellent predictor of long-term development of PrC. For example, the probability of men with a PSA value <1.0 (50% of all men) being diagnosed with aggressive PrC within 15 years is as low as 0.9%. Therefore, screening needs to be performed wisely.

In order to perform more-targetted screening, the Swiss site of the ERSPC has developed a risk calculator to better predict the probability of aggressive disease ('ProstateCheck', Figure 1).

Figure 1: ProstateCheck app for individualising control intervals and reducing overdiagnosis.

The calculator uses important variables, such as free PSA, age, and family history, as well as prostate volume. Besides the predictive properties of the calculator, it also allows urologists and general practitioners to prolong the individual control interval for up to 7 years. With this step, overdiagnosis will be reduced in up to 30-40% of men.

Identify co-existing, occult, high-grade cancer at diagnosis

Once the biopsy is completed and specimens are available, determining the grade and extent of the tumour are essential in order to qualify for AS and to avoid treating microfocal disease. In young men, only those with a true Gleason score of 6 can be included and the strongest John Hopkins (Epstein) criteria need to be entirely fulfilled. In addition, we have learned from the data of the National Swedish Prostate Cancer Registry that the tumour size must not exceed 8 mm in total for young AS candidates. Also, multiparametric magnetic resonance imaging (MRI) is obligatory in order to exclude anterior tumours and to perform a targetted biopsy,

if necessary. This must be done during the early-detection phase in order to exclude a 'wolf in sheep's clothing'.

Trigger points: be aware of the impending tsunami

Monitoring of the candidate is an important task and trigger points of progression must not be missed. A PSA doubling time <3 years has been shown to characterise progression but not its lack of specificity (50%). MRI during follow-up has an important role, but at the moment it is unable to serve as a substitute for the control biopsies of the prostate. To decrease the harms of PSA-based screening, a reduction in overdiagnosis is possible by using risk calculators and prolonging control intervals (i.e. ProstateCheck). Also, stringent AS criteria in young men can help to reduce the harms of screening.

RISK OF THROMBOEMBOLIC DISEASE IN MEN WITH PROSTATE CANCER ON ANDROGEN DEPRIVATION THERAPY: A FOLLOW-UP STUDY IN PCBaSe SWEDEN

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Androgen deprivation therapy (ADT) is the first line of treatment for disseminated prostate cancer (PrC). Alongside its therapeutic benefits, ADT is associated with a number of adverse events (AEs), including decreased insulin sensitivity, changes in lipid profiles, cardiovascular disease, and thromboembolic diseases (TED).[1-5] To date, the association between ADT and TED remains controversial as recent surgeries and disease progression are strongly confounding factors that could not be accounted for in previous analyses.[1,2,4,5]

In an attempt to elucidate the independent influence of ADT on the risk of TED, we investigated the risk of TED in a cohort of 42,263 PrC men on ADT compared with an age and residency-matched PrC-free comparison cohort of 190,930 men in the updated PCBaSe Sweden 3.0, which includes detailed information on filled drug prescriptions, recent surgeries, and disease progression.[3,6] Associations between ADT and deep venous thrombosis (DVT) or pulmonary embolism were analysed using multivariate Cox proportional hazard regression models. History of PrC-related surgeries and the following proxies for disease progression were accounted for: transurethral resection of the prostate, palliative radiotherapy, and nephrostomy.[3] Our findings were reported as a poster presentation at the EAU Congress 2015.

Between 1997 and 2013, 11,242 PrC men received anti-androgen (AA) monotherapy, 26,959 received gonadotropin-releasing hormone (GnRH) agonists, 1,091 received combined androgen blockade, and 3,789 underwent orchiectomy. GnRH agonist users and men who underwent orchiectomy were at an increased risk of TED versus the comparison cohort: hazard ratio (HR) of 1.61 (95% confidence interval [CI]: 1.15-2.28) and 1.67 (95% CI: 1.40-1.98), respectively. Risk of pulmonary embolism was increased in those who switched from AA to GnRH agonists: HR of 2.55 (95% CI: 1.76-3.70).

This increased from 2.52 (95% CI: 1.54-4.12) in Year 1 to 4.05 (95% CI: 2.51-6.55) in Year 2. Risk of DVT was also increased, albeit with no marked rise over time. Additionally, proxies of disease progression were associated with an increased risk of TED. For example, risk of DVT comparing PrC men who underwent nephrostomy versus those who did not: HR of 5.51 (95% CI: 3.75-8.11).[2]

When accounting for surgeries and disease progression, there was a consistently increased risk of TED in men on systemic ADT. However, risk among men on ADT was highest for those who switched from AA to GnRH agonists, which itself is a marker for disease progression. Previous surgeries, disease progression, and ADT may thus all contribute to the risk of TED. Our data suggest that men with PrC and on ADT should be assessed for risk of thromboembolic AEs, especially over long-term treatment periods.

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OUTCOMES OF RADICAL PROSTATECTOMY IN PATIENTS WITH PREVIOUS TRANSPLANTATION

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During the 30th EAU Annual Congress in Madrid this year, we presented a poster of the results of radical prostatectomy (RP) in patients with a previous solid-organ transplantation (Tx). Literature on this topic is sparse due to the small caseload of these patients in single centres.

We conducted a retrospective analysis of peri and post-operative outcomes and tumour-specific morbidity and mortality in Tx patients following RP. We identified 30 patients from our institutional database with biopsy-proven prostate cancer (PrC). Each RP was performed between 1996 and 2014 following Tx (kidney Tx: n=20, heart Tx: n=5, liver Tx: n=5) at our high-volume centre. The median follow-up was 45 months. Post-operative complications were assessed using the Clavien–Dindo classification.

The median age at PrC diagnosis was 64 years (range: 51-73 years). Median pre-operative prostate-specific antigen concentration at diagnosis was 5.3 ng/ml (range: 1.0-250.0 ng/ml). Median intra-operative blood loss was 600 ml (range: 100-1,600 ml) and median operating time was 180 min (range: 120-285 min). Major post-operative complications (Clavien ≥III) occurred in three (10%) cases, all of which were kidney Tx patients. After surgery, the rate of urinary continence at 12 months was 70.0% (n=21) when using a 'no-pad' definition. Biochemical recurrence-free survival was 70.0%. There was no evidence of metastasis or cancer-specific death in recurrent patients. Overall survival was 86.6%.

Using the data included in our poster, we could show that RP in Tx patients is technically feasible. However, performing surgery in these patients can be challenging: multiple previous surgeries can increase the risk of peri-operative complications due to excessive scarring and adhesions. Our results show that RP can be confidently performed without an increased risk of complications.

Histopathological evaluation revealed the disease characteristics of the current RP series. Immunosuppressive therapy does not seem to lead to an increased rate of tumour progression.

RACIAL DISPARITIES IN THE SURGICAL CARE OF LOCALISED PROSTATE CANCER

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Extensive evidence suggests that race and ethnicity strongly correlate with survival following a prostate cancer (PrC) diagnosis. Specifically, cancer-specific mortality has been reported to be higher in African American men with localised PrC compared with their non-Hispanic white counterparts. The underlying reasons are unclear, but are likely to result from complex biological, cultural, and sociodemographic differences. Moreover, some studies indicate a substantial disparity in the quality of received care of racial and ethnic minorities, as well as inconsistency in outcomes of treatment. As black men are less likely to receive definitive therapy in the treatment for PrC than white men, hypothetically causing a large part of care disparities, we restricted our cohort to surgical candidates, hoping to attenuate the effect of unmeasured sociodemographic and cultural confounders.

Using the most recent version of the Surveillance, Epidemiology, and End Results-Medicare linked database, we analysed 26,482 men with localised PrC who underwent radical prostatectomy (RP) within the first year of PrC diagnosis. For each patient we assigned age, year of diagnosis, population density, marital status, college education, income, region, Charlson comorbidity index, Gleason score, and clinical cancer stage, grade, and risk group. Process and quality of care measures included time to treatment, the use of additional cancer therapies (radiotherapy, androgen deprivation therapy), lymph node dissection, and costs. Further outcome measures consisted of complications, emergency department visits, readmissions, short-term mortality, and PrC-specific and all-cause mortality. Multivariable conditional logistic regression, quantile regression, and Cox proportional hazards regression (adjusted for all covariates) were used to model the association of racial disparities with process of care and outcome measures. The effect of comorbidities on survival was estimated with Cox proportional hazards modelling and the weights for the individual comorbid conditions were comprised by coefficient estimates of the condition indicators. Variation in treatment patterns between local treatment areas were accounted for by using health service area clustering.

In conclusion, we observed compelling evidence for the existence of a substantial difference in the quality of surgical care of PrC in black men. African American men treated with RP were more likely to experience adverse events (treatment delay, less lymph node dissection, more post-operative complications, transfusions, emergency department visits, readmissions) and incur higher costs compared with non-Hispanic white men. However, this did not translate into different PrC-specific or all-cause mortality. The observed racial disparities in adverse events following a diagnosis

of localised PrC may be the consequence of access-to-care barriers and selection bias in recommending definitive treatment. Public and professional awareness needs to be raised in order to address these concerning issues and identify their underlying causes.

GENERATION OF PATIENT-DERIVED, THREE-DIMENSIONAL SPHEROID CULTURES FOR *IN VITRO* STUDIES ON LOCALISED PROSTATE CANCER

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Despite considerable advances in recent years, prostate cancer (PrC) research is still hampered by a paucity of realistic *in vitro* and *in vivo* model systems that adequately illustrate natural cancer behaviour. This is especially evident for the clinical setting of organ-confined PrC, as all commonly used PrC cell lines were generated from metastases and do not faithfully retain this clinical phenotype.[1] The use of three-dimensional spheroid cultures derived from primary cancer tissue seems to be a promising approach to overcome several limitations inherent with conventional two-dimensional adhesion cell culture,[2-4] but such a system still needs to be established for organ-confined PrC.

Therefore, we used a novel method to generate patient-derived, three-dimensional spheroid cultures in order to model localised PrC.[5,6] In a first set of experiments, we successfully cultivated and characterised spheroids from 12 cases of organ-confined PrC with a focus on high-risk disease. Immediately after removal in the operating room, radical prostatectomy specimens were put on ice and transferred to an experienced uropathologist who resected a small piece of histologically confirmed (haemotoxylin and eosin [HE]-stained frozen sections) cancer tissue. This piece of tissue was further processed by mechanical disintegration using scalpel and forceps as well as visually controlled, limited enzymatic digestion with a blend of collagenase and non-collagenase proteases. After serial filtration steps, several spheroid populations per sample were cultivated in suspension culture using low-attachment plates in combination with an optimised stem cell medium. We were able to successfully generate and cultivate spheroids from all included cases. Live–dead assays on the basis of differential fluorescent labelling proved that the majority of cells within the spheroids were vital for months. This could be further confirmed by colourimetric assays that were adapted to this cell culture system. Moreover, we were able to show that the spheroids are still vital after freezing in liquid nitrogen and thawing. This will allow long-term cryopreservation and biobanking.

Immunofluorescent staining of the patient-derived spheroid cultures showed Ki67 proliferation indices of 3%, as well as expression of the androgen receptor in the majority of cells. Staining of the luminal cell marker CK8 and the basal cell marker CK5 was quite heterogeneous, suggesting the presence of different cell populations. Using a conventional ELISA assay, markedly elevated PSA levels (up to >200 ng/ml) could be measured in the spheroid culture media, demonstrating a preserved secretory function of the cells.

In the future we will expand our method to a broader spectrum of disease stages. Moreover, additional work is necessary to further molecularly characterise the patient-derived spheroids and to test their applicability for functional tests. We also aim to evaluate the ability of these primary spheroid cultures to predict a therapeutic response of the corresponding patient, including the study of resistance mechanisms or of combination treatment.

Another promising approach will be the development of a co-cultivation system in which patient-derived spheroids are combined with cancer-associated fibroblasts or other components of the tumour microenvironment to study the mechanisms of tumour–stroma interaction. Finally, nude mice xenografts of patient-derived spheroids will complete a personalised, combined *in vitro/in vivo* model of PrC.

The discussion following the presentation of our work primarily focused on methodological details like the composition of the culture medium or the enzymes used for tissue digestion. Another point from one of the session chairs was their concern that these spheroids might mainly contain non-malignant stromal and epithelial cells and therefore not really represent a PrC cell population. A control for malignancy might be necessary to exclude the presence of benign prostate basal or other non-malignant cells. To meet this point, we pointed to the HE-stained, freshly frozen sections we prepared from each tissue sample to ensure a sufficient proportion of cancer cells within them. Apart from that it might even be an advantage of our spheroid cultures that they contain not only cancer cells but also non-malignant constituents of the surrounding tissue, thereby more realistically representing the situation in humans. Nonetheless, it was worthwhile advice to additionally analyse cancer-specific molecular traits such as AMACR overexpression,[7] or the presence of gene rearrangements such as *TMPRSS2-ERG,*[8] which we will include in our future work.

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DO ANTIDIABETIC DRUGS INFLUENCE PROSTATE CANCER AGGRESSIVENESS AND PROGRESSION?

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There is evidence that Type 2 diabetes mellitus (DM) is associated with various forms of cancer, a higher incidence of cancer, and worse cancer prognosis. In prostate cancer (PrC), the role of DM and antidiabetic drugs remains controversial. Moreover, convincing molecular mechanisms describing the influence of antidiabetic drugs on cancer are lacking. Therefore, the aim of this study was to evaluate the impact of DM and antidiabetic drugs in PrC patients. We retrospectively analysed 167 patients diagnosed with both DM and PrC who underwent radical prostatectomy (RP) in the Department of Urology at our institute. We divided our patient cohort into four PrC antidiabetic treatment groups: metformin users, insulin users, other antidiabetic drug users, and those with no antidiabetic drug use (control group), and analysed differences in PrC aggressiveness and laboratory parameters between these groups. In addition, we generated a tissue microarray (TMA) from RP specimens for analysis of candidate target pathways of antidiabetic drugs by immunohistochemistry (IHC). Analysing both biopsy and RP histopathology, we observed that

the Gleason score did not differ significantly between the different treatment groups, and biopsy undergrading did not differ either.

Concerning histology, only positive resection margins were significantly favourable in the metformin user group compared with the control group. Prostate-specific antigen (PSA) and free PSA levels were similar between treatment groups. In addition, C-reactive protein, glucose oxidase, alanine transaminase, gamma-glutamyl transpeptidase, lactate dehydrogenase, amylase, haemoglobin, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine measurements did not differ between the treatment groups. Only glycated haemoglobin levels differed significantly between the groups receiving antidiabetic treatment and the control group, confirming the efficacy of treatment and compliance with therapy. Analyses of patient follow-up data revealed that metformin or insulin treatment was not associated with a change in the frequency of biochemical tumour recurrence, or with lower second-line radiation, hormonal, or chemotherapeutic treatment compared with the control group. Analyses of TMAs by IHC revealed that cell proliferation, as measured by Ki67 staining, and mechanistic target of rapamycin (mTOR) pathway activity (phospho-mTOR) was decreased in the group receiving metformin treatment compared with the control group. In addition, we were able to show that expression of both the androgen receptor protein and the epithelial–mesenchymal transition marker E-cadherin were decreased in the metformin group compared with the control group.

In summary, we did not find a relationship between the use of antidiabetic drugs and PrC aggressiveness or progression. However, tumour biology seems to be different among patients receiving different DM treatments.

THE IMPACT OF NOT DETERMINABLE SURGICAL MARGINS AFTER RADICAL PROSTATECTOMY

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At the University Medical Center Hamburg-Eppendorf, all prostatectomy specimens are inked over their entire surface and processed according to the Stanford Protocol. However, in some patients, despite meticulous pathological processing and detailed surgeon–pathologist consultation, the contact of tumour cells at the inked margin of the radical prostatectomy (RP) specimen remains 'not determinable' (ND). Since 2008, the contact, non-contact, and also ND contact of tumour cells at the inked margin of the prostate are considered to represent a positive, negative, and ND surgical margin (PSM, NSM, and NDSM), respectively. To assess the impact of NDSM after RP, we compared biochemical recurrence (BCR) rates and performed univariable Kaplan–Meier and multivariable Cox regression analyses. Patients with positive lymph nodes (pN1) and pathological Stage IV (pT4) were excluded. The following results were presented in our poster at the 30th Annual EAU Congress in Madrid.

We enrolled 8,694 (pT2-pT3b, pN0/pNx) consecutive men who underwent RP between 2008 and 2013 and had complete follow-up data. In 7,373 (84.1%), 1,141 (13.1%), and 180 (2.1%) patients, the final pathological report stated NSM, PSM, and NDSM, respectively. According to Kaplan–Meier analyses, there was a statistically significant difference in BCR rate between the three SM groups. The NDSM group showed the highest BCR rate in patients with pT3a prostate cancer. In a multivariable model, and after adjusting for pre-operative prostate-specific antigen, pathological stage, Gleason score, and tumour volume, SM status remained an independent

risk factor for BCR. Both NDSM (hazard ratio [HR]: 2.1, p<0.001) and PSM (HR: 2.1, p<0.001) were significantly associated with an increased risk of BCR when compared with NSM. No significant difference was found between PSM and NDSM status.

Taken together with our poster, we could demonstrate that an NDSM is rarely diagnosed by the pathologist but is independently associated with a higher risk of BCR when compared with patients with NSM. Therefore, an NDSM should be considered as a PSM and treated accordingly.

NEOADJUVANT DOSE-DENSE MVAC FOR MUSCLE-INVASIVE BLADDER CANCER: EFFICACY AND SAFETY COMPARED WITH CLASSIC MVAC AND GEMCITABINE/CISPLATIN

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Neoadjuvant cisplatin-based chemotherapy for muscle-invasive bladder cancer (MIBC) results in a pathologic complete response (pCR) in 25-40% of patients and an improved survival compared with cystectomy alone. However, the disadvantages are a delay in definitive surgery and considerable toxicity. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) is a 2-weeks-per-cycle MVAC regimen supported by granulocyte colony-stimulating factor. The purpose of our study was to investigate the efficacy and safety of neoadjuvant dd-MVAC. We compared pCR and toxicity related to dd-MVAC with classic MVAC (4 weeks per cycle) and with gemcitabine/cisplatin (GC, 3 weeks per cycle).

In total, 166 patients with non-organ-confined MIBC were included. They had received either dd-MVAC (n=80), classic MVAC (n=35), or GC (n=51) neoadjuvant chemotherapy between 1990 and 2014. pCR was defined as no evidence of residual tumour in cystectomy and lymphadenectomy specimens (ypT0N0). Toxicity data were reviewed and scored according to the Common Terminology Criteria for Adverse Events 4.0.

Following dd-MVAC, 29% of patients had a pCR. This did not differ significantly from pCR rates following classic MVAC (20%, p=0.366) or GC (32%, p=0.845). Observed Grade 3-4 toxicity rates relating to dd-MVAC (32%) and GC (44%) were similar (p=0.202). The toxicity rate for classic MVAC (55%) was significantly higher than for dd-MVAC, both uncorrected (p=0.026) and corrected for patient and tumour characteristics (odds ratio: 2.84, p=0.037). This difference was mainly attributable to a higher incidence of febrile neutropaenia following classic MVAC (20.7%) compared with dd-MVAC (7.6%, p=0.081).

In conclusion, neoadjuvant dd-MVAC therapy resulted in pathological responses similar to classic MVAC and GC treatment in patients with non-organ confined MIBC. dd-MVAC had a toxicity profile similar to GC, but more favourable than classic MVAC. Our results, in addition to the shorter cycle duration compared with MVAC and GC, suggest that dd-MVAC should be the preferred neoadjuvant chemotherapy option for MIBC.

RITONAVIR SYNERGISES WITH CARFILZOMIB TO CAUSE ENDOPLASMIC RETICULUM STRESS AND AUTOPHAGY IN BLADDER CANCER CELLS

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The cisplatin–gemcitabine combination is a mainstay in the treatment of metastatic cancer, but a new therapeutic approach is needed because its efficacy is limited and there is no curative treatment for metastasised advanced bladder cancer. Our laboratory at the National Defense Medical College has been developing a novel treatment for advanced urological malignancies (renal cancer, prostate cancer, and bladder cancer): killing cancer cells by using combinations of clinically available drugs to cause unfolded protein accumulation, thus inducing endoplasmic reticulum (ER) stress. Unfolded proteins are often repaired by molecular chaperones such as heat shock protein 90, but if the repair fails the unfolded proteins are ubiquitinated and rapidly degraded by the proteasome. Unfolded proteins will therefore not accumulate without simultaneous inhibition of the molecular chaperones and the proteasome. In our previous research we used histone deacetylase inhibitors or HIV protease inhibitors to inhibit molecular chaperones, and used various proteasome inhibitors to inhibit the proteasome.

In the present study we have used bladder cancer cells (UMUC3, HT-1376, 5637) to investigate the efficacy of the combination of the HIV protease inhibitor ritonavir and the novel proteasome inhibitor carfilzomib. The combination inhibited bladder cancer growth synergistically (combination indexes <1) and suppressed colony formation significantly. It induced drastic apoptosis and this apoptosis seemed to be caspase-dependent because the pan-caspase inhibitor Z-VAD-FMK decreased the number of annexin-V-positive cells. As expected, the combination synergistically caused ubiquitinated, unfolded protein accumulation and ER stress. We found that it also synergistically increased the expression of two mammalian target of rapamycin (mTOR) inhibitors, AMP-activated protein kinase and sestrin-2, thereby suppressing the mTOR pathway and causing autophagy (indicated by the increased expression of autophagy marker light chain 3-II). Autophagy is another protein degradation mechanism and, while its role in cancer survival has been controversial, excessive autophagy has reportedly killed cancer cells. Furthermore, we found that the combination induced histone acetylation synergistically. We concluded that the combination of ritonavir and carfilzomib kills bladder cancer cells by synergistically inducing ER stress and autophagy. Histone acetylation is also an important mechanism of the combination's action. The use of the ritonavir-carfilzomib combination is potentially effective in patients who are refractory to treatment with the cisplatin–gemcitabine combination because it acts by completely different mechanisms. We believe that the present study provides a basis for clinical studies of the ritonavir–carfilzomib combination in patients with metastasised advanced bladder cancer.

IMPACT OF FLUORESCENCE-GUIDED BLADDER TUMOUR RESECTION ON SURVIVAL AFTER RADICAL CYSTECTOMY

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The purpose of this study was to investigate whether photodynamic diagnosis (PDD)-guided transurethral resection of a bladder tumour (TURBT) influences the prognosis of patients who undergo radical cystectomy (RC) for bladder cancer (BLC) during the course of their disease.[1] A total of 224 consecutive patients who underwent RC and bilateral pelvic lymphadenectomy for BLC between 2002 and 2010 (median follow-up: 29 months, interquartile range: 8-59 months) were retrospectively investigated to compare outcomes between those who had previously undergone PDD-guided (hexaminolevulinate [HAL] or 5-aminolevulinate [ALA]) TURBT and those who had undergone white-light TURBT (WL-TURBT). Kaplan—Meier analyses were used to estimate recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) using log-rank testing and Cox regression analysis for multivariate analysis. Of the 224 patients, 66 (29.5%) underwent HAL-TURBT, 23 (10.3%) ALA-TURBT, and 135 (60.2%) WL-TURBT prior to RC.

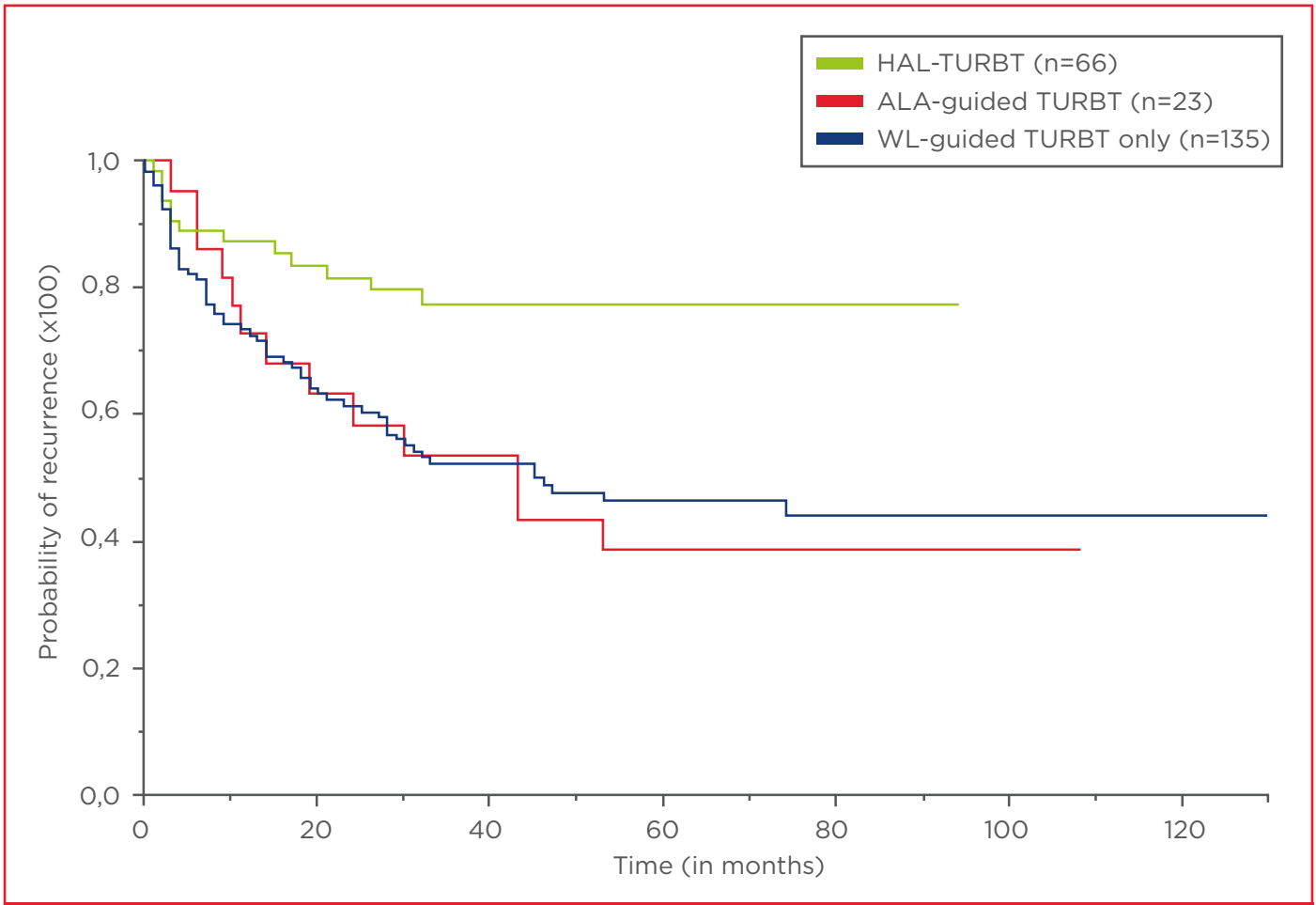

Figure 1: Recurrence-free survival after radical cystectomy (RC) in patients who underwent hexaminolevulinate (HAL)-guided versus aminolevulinate (ALA)-guided versus white light (WL)-guided transurethral resection of a bladder tumour (TURBT) prior to RC.
p=0.002 for HAL versus ALA/WL

The 3-year RFS/CSS/OS was 77.8%/83.9%/74.0% for HAL-TURBT, 53.6%/74.5%/60.9% for ALA-TURBT, and 52.4%/59.7%/56.5% for WL-TURBT (p=0.002/0.023/0.037 for HAL versus WL/ALA, Figure 1). The use of PDD-TURBT was associated with a higher number of TURBTs prior to RC (p<0.001) and a higher number of re-resections (p=0.015), a longer time interval between the first TURBT and RC (p=0.044), and a lower rate of post-operative systemic chemotherapy (p=0.001). In a multivariate analysis, performance of HAL-TURBT, pathologic tumour and nodal stage, as well as soft-tissue surgical margin status remained independent predictors of RFS, CSS, and OS. Taken together, this series suggests for the first time that HAL-TURBT is an independent predictor of improved survival after RC.

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THE INTERVAL BETWEEN DIAGNOSIS AND RADICAL CYSTECTOMY DOES NOT IMPACT THE OUTCOMES OF PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Radical cystectomy (RC) with lymphadenectomy is the mainstay therapy for muscle-invasive bladder cancer (MIBC). Level I evidence supports neoadjuvant cisplatin-based combination chemotherapy in MIBC. However, to date, neoadjuvant chemotherapy (NAC) has not been adopted by the uro-oncological community and may indeed be less commonly used than adjuvant chemotherapy. The exact reasons for these practice patterns remain to be determined, but under-usage of NAC is due in part to the increased time interval between diagnosis and surgery. We aimed to determine if the old cutoff of 12 weeks between diagnosis and RC remains a predictor of outcomes in the NAC setting.

For this purpose, we retrospectively reviewed the records of 935 patients with cT2-4aN0-3M0 urothelial bladder cancer who received at least three cycles of NAC and underwent RC at 19 institutions between 2000 and 2013. NAC data encompassed the type of regimen, number of cycles, time interval between transurethral resection of bladder tumour (TURBT) and start of NAC, and time interval between commencement of NAC and RC. Estimated overall survival (OS) was compared using various time to RC cutoffs (12, 16, 20, and 24 weeks) using the log-rank test. The association between time to RC and overall mortality was evaluated using a multivariable Cox proportional hazards regression model, adjusting for standard, clinical, and pathological factors.

The median time between TURBT and RC was 23 weeks (interquartile range [IQR]: 19-29 weeks). There were 563 patients (58%) who received at least four cycles of NAC, with gemcitabine–cisplatin being the most common regimen (55%). Pathological stage was pT0 in 223 patients (22.9%). Node-positive disease was found in 258 patients (26.5%). Within a median follow-up of 15 months (IQR: 6-34 weeks), 337 patients (34.7%) died. When stratifying the cohort by time to RC, no differences were found in terms of OS using the cutoffs of 12, 16, and 20 weeks. A time to RC >24 weeks was associated with a higher risk of overall mortality (p=0.01, log-rank test). However, in multivariable analysis adjusting for age, gender, type of chemotherapy regimen, number of cycles, pathological stage, and margins status, the 24 weeks cutoff did not retain its association with overall mortality (hazard ratio: 1.24, 95% confidence interval: 0.94-1.63; p=0.13).

In conclusion, an interval of >12 weeks between diagnosis and RC has been associated with overall

mortality in the pre-NAC area. This cutoff does not seem to impact the outcomes of patients treated with NAC and RC in a daily practice setting. Thus, this study advocates in favour of NAC administration in MIBC.

CIRCULATING TUMOUR CELL DETECTION HAS AN INDEPENDENT PROGNOSTIC IMPACT IN HIGH-RISK NON-MUSCLE-INVASIVE BLADDER CANCER

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High-risk non-muscle-invasive bladder cancer (NMIBC) is characterised by a high rate of recurrences and progressions. In particular, there is a recurrence rate of 50-70% and a progression rate of 25-50% following transurethral resection of a primary bladder cancer (TURB) without any adjuvant therapy. After a bladder-sparing treatment, the risk of developing a metastatic disease is up to 15%, and the risk of death within 5 years is approximately 16-23%.[1]

To date, the European Organisation for Research and Treatment of Cancer (EORTC) risk tables are the best-established predictive tool helping in the management of patients with NMIBC. These tables, which allow an easy prediction of recurrence and progression, classify patients by risk (low, intermediate, or high) following the sum of many factors (number of tumours, tumour size, prior recurrence rate, T category, presence of carcinoma in situ (CIS), and tumour grade).[2]

Approved by the FDA, circulating tumour cells (CTCs) in peripheral blood can be identified and counted in order to predict prognosis in metastatic breast, colorectal, and prostate cancer.[3] Some authors have described the presence of CTCs in locally advanced bladder cancer or in a metastatic setting,[4] and it would be interesting to investigate if they are present during the early stages of disease. High-risk NMIBC is a perfect model because of the lack of any biological markers and because of the high incidence of recurrences and progressions. Furthermore, the decision-making process between a conservative treatment, such as TURB followed by adjuvant intravesical therapy, or an aggressive treatment, such as radical cystectomy, is of vital importance.

The aim of this study was to investigate if the presence of CTCs is a good predictor of disease prognosis in a large population of patients with high-risk NMIBC, and who are all candidates for conservative endoscopic surgery.

This was a single-centre trial designed to correlate the presence of CTCs with local recurrence and progression in high-risk NMIBC patients. There were 102 eligible patients (28 patients were excluded due to inadequate samples or Bacillus Calmette-Guérin (BCG) intolerance) who underwent TURB followed by intravesical adjuvant immunotherapy with BCG. Median follow-up was 24.3 months (range: 4-36 months). The FDA-approved CellSearch® System was used to enumerate CTCs. Kaplan–Meier analyses, log-rank tests, and multivariate Cox proportional hazard analysis was applied to assess the association of CTCs with time-to-first-recurrence (TFR), time-to-progression (TTP), and metastasis-free interval (Figure 1).

CTCs were detected in 20 patients (20%) and median CTC number was 1 per sample (range: 1-50). The presence of CTCs predicted both decreased TFR (log rank: p<0.001; multivariate-adjusted hazard ratio [HR]: 2.92, 95% confidence interval [CI]: 1.38-6.18, p=0.005) and TTP (log rank: p<0.001; HR: 7.17, 95% CI: 1.89-27.21, p=0.004).

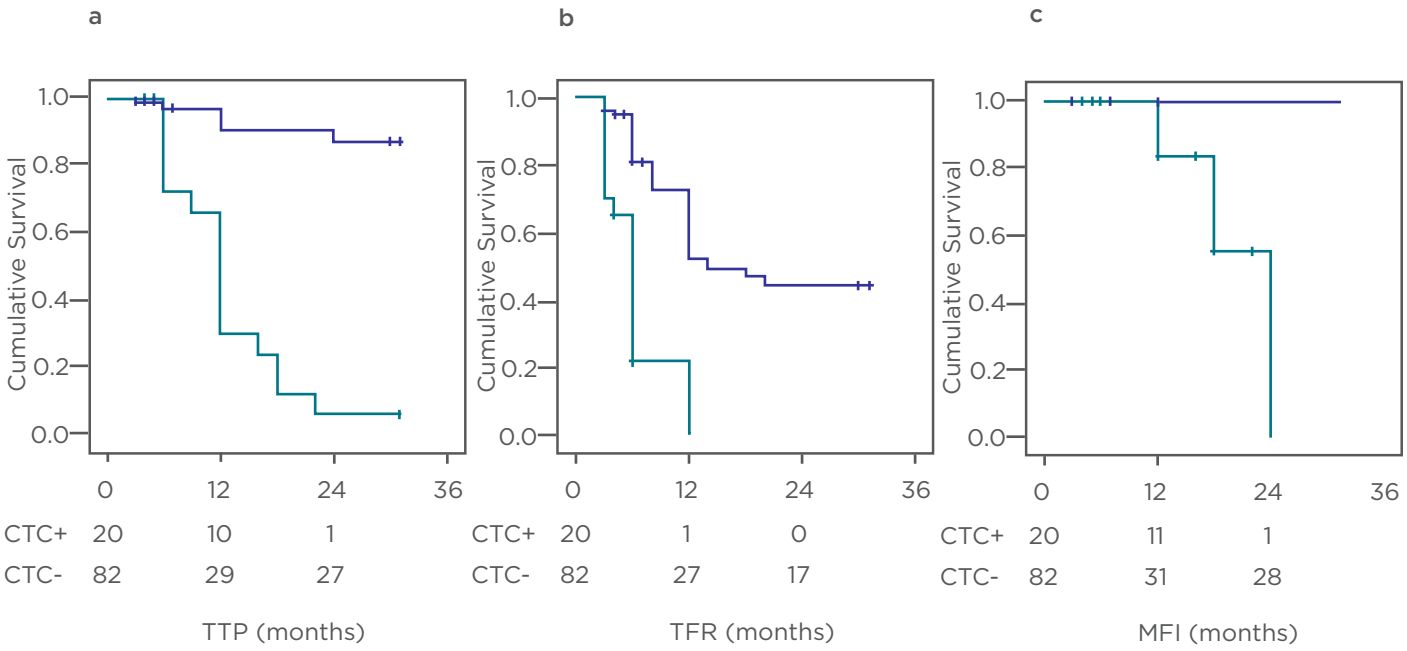

Figure 1: Kaplan–Meier curves comparing CTC+ and CTC– patients.
TTP: time-to-progression; TFR: time-to-first recurrence; MFI: metastasis-free interval; CTC: circulating tumour cell.

During the follow-up period, 43 patients (42%) had local recurrence and 21 patients (20%) experienced progression to muscle-invasive disease, of whom 6 (29%) also progressed to metastatic disease.

Compared with those without CTCs, a significantly greater proportion of patients with CTCs displayed tumour size >3 cm (9 [45%] versus 17 [21%], p=0.023), CIS presence (12 [60%] versus 9 [11%], p<0.001), multifocality (20 [100%] versus 58 [71%], p=0.003), lymph vascular invasion (10 [50%] versus 6 [7%], p<0.001) and appearance of distant metastases (6 [30%] versus 0 [0%], p<0.001).

Analysing the results, CTC presence in our series is a strong indicator that some patients suffering from NMIBC may already have a systemic disease at diagnosis and require a treatment aimed at eradicating systemic tumour cell spread.

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IMMUNOTHERAPY: RENAL CELL CANCER

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The old hypothesis of Thomas Lewis that the primary function of cellular immunity is to "protect from neoplastic disease", which dates back to the late 1950s, is undergoing a renaissance in the treatment of renal cell carcinoma (RCC), making immunotherapy of metastatic RCC (mRCC) the new focus.[1]

Table 1: Overview of available checkpoint modulators for cancer immunotherapy.

Target pathway	Substance	Company
CTLA-4	Ipilimumab	BMS
	Tremelimumab	Pfizer
PD-1	Nivolumab (BMS-936558)	BMS
	Pembrolizumab (MK-3475)	Merck
	AMP-224	Amplimmune
	Pidilizumab (CT-011)	CureTech
PD-L1	MEDI4736	MedImmune/AstraZeneca
	MPDL3280A	Genentech/Roche
	MSB0010718C	MerckSerono
	BMS-936559	BMS
LAG-3	IMP321	Immutep

CTLA-4: cytotoxic T lymphocyte-associated antigen 4; PD-1: programmed death 1; PD-L1: programmed death-ligand 1; LAG-3: lymphocyte activation gene 3.

The central goal in immunotherapy of mRCC is the targetted activation of T cells. The first attempts at immunotherapy of mRCC were a non-specific stimulation of the immune system with cytokines, namely interleukin 2 (IL-2) and interferon alpha. This led to a moderate efficacy, but complete and partial remissions are observed in approximately 12.9% as demonstrated in a recent meta-analysis. Here, about 28% of the reported remissions were complete responders, especially in patients undergoing high-dose IL-2 treatment.[2]

Currently in RCC, a transformation from the traditional non-specific therapy with cytokines to highly specific approaches, which directly target the cancer cells and the tumour microenvironment, can be observed. Several randomised immunotherapy trials have been reported and are underway in the adjuvant or metastatic setting; the two most advanced of these trials are discussed below.

AGS-003 (Argos Therapeutics, North Carolina, USA) is a dendritic cell-based vaccine of the patient´s own amplified, antigen-coding tumour RNA and synthetic CD40L RNA. Currently, AGS-003 is being investigated in a Phase III trial in advanced RCC patients (ADAPT, n=450) randomised to AGS-003 plus sunitinib versus sunitinib alone as a first-line treatment (NCT01582672).

IMA901 (Immatics, Tübingen, Germany) is a synthetic peptide vaccine consisting of nine fully defined tumour-associated antigen (TAA)-derived T cell epitopes. A total of 68 human leukocyte antigen (HLA) A*02-positive mRCC patients with at least one previous therapy were randomised to receive single-dose cyclophosphamide (Cy, 300 mg/m^2) versus no pre-treatment 3 days prior to the start of IMA901 + granulocyte—macrophage colony-stimulating factor (75 µg). Progression-free survival was similar in both study groups (+Cy versus —Cy), but for median overall survival there was a trend for a prolonged survival in the +Cy arm versus the —Cy arm (23.5 versus 14.8 months, hazard ratio [HR]: 0.57, p=0.090; NCT00523159).[3] Currently, IMA901 is being investigated in the IMPRINT Phase III trial, in which 340 HLA-A*02-positive patients have been randomised in a 3:2 ratio to receive IMA901 plus sunitinib versus sunitinib alone as a first-line treatment for metastatic clear cell RCC (NCT01265901).

The results of these trials are promising, but none of the vaccines have gained regulatory approval for marketing in Europe or the USA despite ongoing Phase III trials for AGS-003 and IMA901. Unfortunately, the immune system can be controlled and influenced by local or systemic environments to prevent an effective T cell activation at checkpoints of T cell activation. Here,

the programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) axis is the most heavily explored pathway in RCC.

Checkpoint inhibition: PD-1/PD-L1 axis

PD-1 is a key immune checkpoint receptor expressed by activated T cells, where it terminates immune responses upon antigen stimulation to avoid massive immune-mediated destruction. Anti-PD-1 antibodies, such as nivolumab (BMS-936558, Bristol-Myers Squibb, New York City, New York, USA), pembrolizumab (MK-3475, Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, USA), AMP-224 (MedImmune/AstraZeneca, London, UK), pidilizumab (CT-011, Curetech, Yavne, Israel), and anti-PD-L1 antibodies, such as BMS-936559 (Bristol-Myers Squibb, New York City, New York, USA), MPDL3280A (Genentech/Roche, Basel, Switzerland), MEDI4736 (MedImmune/AstraZeneca, London, UK), and MSB0010718C (MerckSerono, Darmstadt, Germany), are in different stages of pre-clinical and clinical development Phase I-III studies in RCC cancer entities (Table 1).

Nivolumab, a fully humanised anti-PD-1 antibody, has shown anti-tumour activity in a Phase I study with 296 solid-cancer patients; among these, 33 had mRCC and received doses of either 1 or 10 mg/kg. The objective response rate was 4 of 17 patients (24%) treated with the 1 mg/kg dose, and 5 of 16 (31%) patients treated with the 10 mg/kg dose. Five out of eight patients had a response longer than 1 year. Stable disease was observed in an additional nine (27%) patients.[4] Based on these results, a large Phase III trial of 822 patients with metastatic or advanced RCC in the second-line setting was initiated (CheckMate 025, nivolumab versus everolimus). The study has terminated recruitment and is currently in follow-up (NCT01668784).

At ASCO 2014, additional study data from a dose-escalation trial, a combination study of nivolumab with a tyrosine kinase inhibitor (TKI), and of nivolumab with ipilimumab were presented. In the dose-ranging Phase II study of nivolumab, the objective response rate was not different between the groups (20-22%; 0.3, 2, and 10 mg/kg).[5] In a Phase II study, nivolumab was combined with the TKI sunitinib or pazopanib in mRCC. The efficacy was higher in the combinations than anticipated for the single agents, but severe adverse events (AEs) at Grade 3 or 4 occurred in 82% of the nivolumab plus sunitinib arm, and in 70% of the nivolumab plus pazopanib arm.[6]

In another Phase I study, patients were treated with combinations of nivolumab and ipilimumab. Combination therapy was either nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=21) or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=23). Responses were higher with the combinations than was previously reported for each monosubstance.[7] The encouraging results of this Phase I study led to the initiation of a Phase III study of first-line treatment in mRCC patients, with the combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg compared with sunitinib monotherapy (CheckMate 214, NCT02231749).

Conclusion

Checkpoint inhibition with nivolumab and ipilimumab demonstrated a prolonged overall survival for melanoma patients and it is anticipated that this will also be achieved in mRCC patients. Nevertheless, this 'manipulation' of the immune system also leads to new, probably class-specific, immune-related AEs that might be dose-limiting.[6] Although checkpoint inhibitors are classified as specific immunotherapy, it has to be stressed that only the mode of action is specific, e.g. the target receptor is well defined. For the future, these facts warrant that checkpoint modulators are not only to be used as stand-alone drugs, but rather in combination with a vaccination-specific approach in which the immune response is directed against specific TAAs.

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ANALYSIS OF PD-L1 EXPRESSION DATA FROM THE TCGA KIDNEY RENAL CLEAR CELL CARCINOMA STUDY: ARE THERE RECOMMENDATIONS FOR 2ND GENERATION IMMUNOTHERAPY CONCEPTS?

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The *CD274* gene product B7-H1 (programmed death ligand 1, PD-L1) and its receptor (programmed death 1, PD-1) are targetted by 2nd generation immunotherapy in T cells and clear cell renal cell carcinoma (ccRCC) cells using therapeutic antibodies against the receptor and ligand proteins.[1,2] Increased expression of PD-L1 on tumour cells and tumour-infiltrating lymphocytes (TILs) is reported to be a negative prognosticator for ccRCC[3] and may lead to inactivation of the T cell-mediated host immune response to the tumour,[4] which provides a rationale for 2nd generation immunotherapy in advanced or metastasised ccRCC.

Varying response rates to anti-PD-1 therapy have been reported, raising the question of whether heterogeneous expression of PD-L1 and PD-1 in ccRCC could explain these diverse responses. We analysed 'The Cancer Genome Atlas' (TCGA) Kidney Renal Clear Cell Carcinoma (KIRC) study results, which included molecular data from 479 ccRCC patients,[5] for mRNA expression of PD-L1 and its associations with adverse clinicopathological parameters and survival.

The mRNA expression data from the primary tumours did not show significant associations between PD-L1 and the status of metastasis, tumour stage, and grade; moreover, subset analyses of paired tumour and normal tissues from 69 ccRCC patients revealed no tumour-specific increase in PD-L1 (p=0.263). Interestingly, multivariate Cox regression survival analyses showed that higher PD-L1 mRNA expression levels in tumours might be associated with improved survival of patients (HR=0.59, p=0.006).

Therefore, the TCGA KIRC data are in line with previous results describing PD-L1 as a positive prognosticator for colorectal, breast, and lung cancers. Thus, these results scrutinise the rationale for using 2nd generation immunotherapy in ccRCC, which is based on the assumption that PD-L1 is a negative prognosticator. Furthermore, expression of the receptor protein PD-1 is found in TILs but also in tumour cells of a large majority of ccRCCs (proteinatlas.org), potentially affecting their response to immunotherapeutic approaches.

In conclusion, these results indicate the importance of evaluating which PD-1 and/or PD-L1 expression phenotypes detected in primary tumours or metastases are associated with a gain, or even loss, in survival following 2nd generation immunotherapy.

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LOWER URINARY TRACT DYSFUNCTION: WHAT IS NEW AT EAU 2015?

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Lower urinary tract symptoms (LUTS) represent one of the most common clinical complaints in adult men and women. At the 30th EAU Annual Meeting in Madrid there were 137 abstracts presented in the field of LUTS during eight poster sessions.

Stress urinary incontinence (SUI) is an extremely common complaint in every part of the world, and it causes a great deal of distress and embarrassment to patients. Mid-urethral slings are now the most frequently used surgical intervention for women with SUI in Europe. Long-term follow-up of patients after the treatment of SUI is very important for the evaluation of efficacy and safety. Bock et al. presented data describing 10 years of follow-up after treatment with tension-free vaginal tapes (TVTs). More than 97% of these patients reported no SUI at 2 years, 5 years, and 10 years of follow-up. There was a sharp decline in the degree of nocturia at the 2 years timepoint, although it only reached baseline levels after 10 years of follow-up. At baseline, urgency was reported by 62%, and this number dropped to 18% at 2 years and increased steadily thereafter to 32% (5 years) and 41% (10 years). Despite having an almost perfect outcome, many women develop overactive bladder (OAB) symptoms 5-10 years after the procedure, which may contribute to an unsatisfactory long-term outcome. There is continued innovation aimed at reducing the invasiveness of procedures for SUI.

Single-incision mid-urethral slings have been introduced on the basis of providing mid-urethral support using a variety of modifications to a short macroporous polypropylene tape. Dr Tutolo presented data describing 5 years of follow-up and the outcomes of a prospective trial comparing a transobturator mid-urethral sling (Monarc) with a single-incision mini-sling (Miniarc). Despite similar results of the dry rates (87% versus 89%) in the treatment of SUI, there was a significant difference in OAB-free survival in favour of transobturator slings. Dr Kocjancic presented 2-year follow-up outcomes for a novel single-incision sling for the treatment of female SUI. The Altis® sling is an adjustable, single-incision device, and, according to the results of the study, almost 81% of women were continent in the 2 years following surgery.

Voiding dysfunction is an adverse effect of anti-incontinence procedures and may require further intervention, such as clean, intermittent self-catheterisation. One possible cause is overcorrection of the anatomical deformity by the sling. Obstructive voiding after TVT slings might be managed with sling release. Baekelandt reported satisfactory long-term functional results after unilateral mid-urethral sling release for voiding dysfunction with a continence rate of 73.9% at 6 months.

Antimuscarinic drugs are currently the mainstay of treatment for urge urinary incontinence. However, it is recognised that, in clinical practice, many patients stop taking their medication. More recently, research has focused on β-adrenoceptor stimulation as a means of increasing detrusor relaxation and therefore improving urine storage symptoms. Mirabegron, a new β3-adrenomimetic agent for the treatment of OAB, shows promising results in everyday practice. Wagg and co-authors investigated the compliance rate with mirabegron in comparison with traditional antimuscarinics for 12 months after starting the treatment. Compliance was numerically higher with mirabegron than with solifenacin, tolterodine (extended-release), and oxybutynin (immediate release) at all timepoints. However, the number of patients taking mirabegron was significantly lower compared with other medications.

Botulinum toxin (BTX) injections into the bladder wall are being increasingly used to treat persistent or refractory urinary incontinence. Dr Drake reported the results of a large post-hoc analysis of two major BTX A (BTXA) studies that showed this treatment is effective irrespective of incontinence severity at baseline. At the same time, De Ridder and co-authors investigated the durability of BTXA in OAB – an extension study of 543 patients, with a little over half of the patients

completing the study (51.2%). The authors concluded that, regardless of the number of treatments, a high proportion of the patients reported benefits with no new safety issues.

In conclusion, the long-term results of TVT are still compelling but, at the same time, concomitant OAB may compromise patients' satisfaction with the procedure. Comparative studies showed that single-incision slings are not inferior to conventional mid-urethral slings for the treatment of female SUI, but they may cause more storage symptoms. Onabotulinum toxin type A appears to be effective in the long term, regardless of the severity of initial symptoms. Extension of the treatment revealed no additional adverse events. The use of the β3-adrenomimetic mirabegron is associated with greater compliance among patients with OAB when compared with the use of antimuscarinics.

NOCTURIA, NOT ONLY AFTER WETTING YOUR WHISTLE?

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Nocturia, or waking up at night to void, is typically categorised as a storage lower urinary tract symptom (LUTS), which assumes disorders of the lower urinary tract as the underlying cause. However, recent research shows that nocturia differs from other LUTSs because of its multifactorial aetiology, with underlying disorders sometimes unrelated to lower urinary tract dysfunctions. Therefore, nocturia may be regarded as a condition in its own right.[1,2]

Is nocturia a symptom or a disease?

Nocturia can be considered as a bothersome complaint caused by lower urinary tract disorders, sleep disorders, or global or nocturnal polyuria. On the other hand, nocturia can also be considered as a disease that needs to be treated because of the associated morbidity and perhaps mortality.[1,2] Long-term follow-up of children with nocturnal enuresis (NE) shows that approximately one-third also experience nocturia in adulthood. This finding supports the theory that both conditions have a similar pathophysiology, and that curing NE does not necessarily lead to a resolution of the underlying pathophysiological condition.[3] Thus, nocturia is a bothersome systematic symptom that occurs as a result of a wide range of underlying conditions that need to be diagnosed (e.g. lower urinary tract disorders, obstructive sleep apnoea syndrome [OSAS], heart failure, and diabetes).

Is nocturia caused by disorders in bladder or kidney function?

Before therapy can be started, differentiation between a reduced functional bladder capacity and (nocturnal) polyuria is indicated. This requires a comprehensive diagnostic approach that involves anamnesis, questionnaires, and frequency–volume charts.[4] This approach also allows physicians to explore for underlying systemic diseases.

Is (nocturnal) polyuria caused by abnormalities in sodium or water diuresis?

A more detailed diagnostic approach involving renal function profiles may be helpful to subtype patients with (nocturnal) polyuria. By analysis of multiple daytime and nighttime urine samples, this test is able to identify disorders in sodium and water diuresis. Clinical studies demonstrate that a proportion of patients with nocturnal polyuria have an increased nocturnal sodium excretion,[5] which has been linked to salt sensitivity and hypertension.[6]

Can we optimise treatment of nocturia?

Future clinical trials need to assess the effect of treating nocturic patients according to the underlying pathophysiology in order to find the most effective and safe treatment for each patient subtype. Treatment options include antimuscarinics in cases with reduced functional bladder capacity, desmopressin for patients with

an increased nocturnal water diuresis, diuretics for patients with an increased nocturnal sodium diuresis, and continuous positive airway pressure for patients with OSAS.

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BLADDER WALL THICKNESS IS PREDICTIVE OF DETRUSOR OVERACTIVITY IN MALE PATIENTS WITHOUT EVIDENCE OF BENIGN PROSTATIC OBSTRUCTION: RESULTS FROM A MULTICENTRE COHORT

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The assessment of bladder wall thickness (BWT) and detrusor wall thickness (DWT) in the management of male patients with lower urinary tract symptoms (LUTS) is still controversial. Previous studies reported a significant correlation between increased BWT/DWT and the detection of bladder outlet obstruction (BOO) in male patients with LUTS who underwent pressure-flow studies.[1,2] Nevertheless, the lack of standardisation has limited the worldwide diffusion of this technique and the latest European Association Guidelines still consider BWT/DWT investigational in the assessment of male LUTS. The evaluation of BWT with a transvaginal approach was widely employed in female patients with LUTS to predict the incidence of detrusor overactivity (DO), with a BWT threshold of 6 mm considered highly suggestive of DO.[3] In contrast, no previous study has investigated a possible correlation between increased BWT/DWT and the presence of DO in male patients with LUTS; our study is the first to explore this association.

We enrolled 600 male patients with LUTS secondary to benign prostatic enlargement (BPE) in two tertiary hospitals. Patients underwent a standard diagnostic assessment of LUTS that included family history, physical examination, prostate specific antigen measurement, uroflowmetry, prostate volume, and the evaluation of post-voiding residual volume. Furthermore, for each patient we performed the assessment of BWT according to Manieri's technique and a pressure-flow study.[4] To avoid the possible effect of BOO on BWT, we excluded patients with Schaëfer Class ≥2 from the study, and we therefore retrospectively analysed data from 196 patients (98 with DO and 98 without DO).

We found no significant difference in the evaluated parameters between the two groups, except the BWT. Patients with DO presented with a significantly thicker bladder wall when compared with patients without DO (4.3 mm versus 3.6 mm, p=0.001). This finding was also confirmed in multivariate analysis: BWT was a statistically significant predictor of DO (odds ratio: 2.17 per mm, confidence interval [CI]: 1.4-3.1; p=0.001). Moreover, evaluation of the prognostic value of BWT for the diagnosis of DO in our patient population by receiver operating characteristic (ROC) analysis showed a good prognostic index. The shape of the ROC curve for BWT had the typical graphical characteristics of good prognostic parameters, as shown by the high value of the area under the ROC curve (0.71, CI: 0.59-0.75). According to our results, BWT could be an effective non-invasive

predictor of DO in male patients with LUTS and with no evidence of BOO.

Notwithstanding a delta of 0.7 mm in patients with and without DO, our results may appear statistically significant but not clinically relevant; according to previous studies, the inter and intra-observer variability in the evaluation of BWT is 0.12 mm and 0.57 mm, respectively. However, the main aim of our study is not to recommend BWT as an alternative method to pressure-flow studies for the diagnosis of DO in male patients with LUTS. Our results should be confirmed in a larger, prospective study that would have the merit of us being able to hypothesise and observe for the first time whether BWT in male patients is related not only to BOO but can also reflect the presence of DO. If our hypothesis is confirmed in further studies it can increase the value of a BWT evaluation in the prediction of the presence of BOO in male patients with LUTS and with possible DO. Our results showed that DO and BOO could contribute equally to the increase in BWT observed in male patients with LUTS and BPE, and therefore the role of BWT as a proxy of BOO could be arguable and further investigated in patients with DO.

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THE EXCITING UROTHELIUM

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A recent focus of current lower urinary tract research has been afferent mechanisms, and the processes by which afferent information is generated and conveyed to the central nervous system (CNS) in the control of micturition. One of the pathways defined involves the bladder mucosa, but attention has been given mainly to the urothelium. The urothelium, which lines the inner surface of the renal pelvis, the ureters, and the urinary bladder, not only forms a high-resistance barrier to ion, solute and water flux, and pathogens, but also functions as an integral part of a sensory web that receives, amplifies, and transmits information about its external milieu. Urothelial cells have the ability to sense changes in their extracellular environment, and respond to chemical, mechanical, and thermal stimuli by releasing various factors, such as adenosine triphosphate, nitric oxide, and acetylcholine. They express a variety of receptors and ion channels, including P2X3 purinergic receptors, nicotinic and muscarinic receptors, and transient receptor potential channels. All of these have been implicated in urothelial–neuronal interactions and involved in signals that can be amplified and conveyed to nerves, detrusor muscle cells, and ultimately the CNS via components in the underlying lamina propria (LP), such as interstitial cells. Alterations in urothelial-cell signalling in various bladder pathologies (including the ageing bladder) can lead to symptoms such as urgency, urinary incontinence, nocturia, and even impaired bladder emptying.

The urothelium plays a critical role as a permeability barrier to urine, and an intact barrier is a prerequisite for normal afferent signalling from the bladder. The ability of the bladder to maintain a barrier, despite large alterations in urine volume and increases in pressure during bladder filling and emptying, is dependent on several features of the outer umbrella cell layer. These features include tight-junction complexes that reduce the movement of ions and solutes between cells and specialised lipid molecules and proteins in the apical membrane, which reduce the permeability of the cells to small molecules. During bladder filling, the umbrella cells become flat and squamous. This shape change is accompanied by vesicular traffic

(i.e. exocytosis/endocytosis), adding membrane to the apical surface, thereby increasing overall urinary bladder surface area. These processes allow the bladder to accommodate increasing volumes of urine during filling without compromising barrier function.

Modification of the urothelium and/or loss of epithelial integrity in a number of pathological conditions can result in the passage of toxic/irritating urinary constituents through the urothelium, or release of neuroactive substances from the urothelium. This may lead to changes in the properties of sensory nerves and in turn sensory symptoms such as urinary frequency and urgency. Thus, chemical communication between the nervous system and the urothelial cells may play an important role in the generation of urinary bladder dysfunction.

The bladder mucosa, consisting of the urothelium, basement membrane, and underlying LP (the sensory web) works in concert with other components in the bladder wall. The urothelium not only forms a highly efficient barrier to potentially harmful urine components, but also exhibits properties similar to those of nociceptive and mechanoceptive afferent neurons. Activation of the urothelial cells by chemical, thermal, or mechanical stimuli can evoke the release of various mediators or neurotransmitters that can influence nerve activity, detrusor cell contraction, and ultimately bladder function through the sensory web. The LP with its several types of interstitial cells and afferent nerves may act as a coordination centre for bladder activity both during bladder filling (spontaneous activity) and for initiation of the micturition reflex, thus having an important integrative role in signal transduction to the CNS (nociception, mechanosensation). The mucosa undergoes important changes in many bladder diseases, such as bladder pain syndrome, neurological injuries, and bladder overactivity, and is an important target for treatment. We have begun to understand the fundamental properties of the bladder mucosa, which is a rapidly expanding research field with exciting translational possibilities, and considerable progress in this area can be anticipated.

ENDOSCOPIC RENDEZVOUS PROCEDURE FOR URETERAL IATROGENIC DETACHMENT: REPORT OF A CASE SERIES WITH LONG-TERM OUTCOMES

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During the previous EAU Congress (Madrid, 20th-24th March, 2015), and during the poster session on 'Trauma and emergencies in urology', we presented our experience in 'Endoscopic rendezvous procedure for ureteral iatrogenic detachment: report of a case series with long-term outcomes'.

Injury to the ureter is the most common urologic complication of pelvic surgery, with an incidence ranging from 1-10%.[1] Most cases of ureteral injuries are related to gynaecological procedures: in fact, the ureter is particularly vulnerable to detachment or ligation during hysterectomy due to its position from the lateral edge of the cervix. Between January 2009 and April 2013, 18 rendezvous procedures were performed in patients with a complete ureteral detachment.[2,3] We assessed the operative and clinical outcomes achieved in these patients over a mean follow-up of 26.5 months. Computed tomography urography at discharge, and at 6 and 12 months post-surgery, confirmed the restoration of ureteral integrity without any leakage in 66% (12/18) of cases, while showing ureteral stenosis in 22% (4/18) of cases, and ureteral leakage in 12% (2/18) of cases.

The overall long-term success rate for all 18 patients was 78% (14/18) at a mean follow-up of 26.5 months.

The rendezvous technique is an effective, combined radiological and endourological procedure that can be used to manage ureteric injuries in the early post-operative period of cases with appropriate indications. This minimally invasive manoeuvre can restore the continuity of the ureter and reduce the need for open surgical repair that is associated with higher morbidity. We believe that this procedure may represent the optimal initial solution in patients with iatrogenic ureteral lesions, before attempting invasive procedures.

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INTRAVESICAL PROSTATIC PROTRUSION AND BLADDER OUTLET OBSTRUCTION: SUMMARY OF LATEST CONCEPTS

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Intravesical prostatic protrusion (IPP) is the distance between the innermost protrusion of the prostate to its base at the circumference of the bladder, as seen in the sagittal view of a comfortably full bladder. Clinical benign prostatic hyperplasia (BPH) can be defined as an adenoma (or adenomata) that causes varying degrees of obstruction with or without symptoms, and irrespective of size. The disease does not affect the transitional zone or the periurethral zone diffusely, but instead forms discrete nodules that cause obstruction by compression and/or distortion of the bladder outlet. Therefore, the degree of obstruction depends more on the site than the size of the adenoma. The location of the adenoma gives rise to the IPP that distorts the shape of the bladder neck. Therefore, the IPP can be considered as the shape of the prostate.

Clinical BPH (prostate adenoma [PA]) can be diagnosed non-invasively by transabdominal ultrasound, scanning for IPP, and uroflowmetry. The presence of an IPP has 100% specificity and 100% positive predictive value in the diagnosis of PA. For individualised treatment, patients with PA can be phenotyped according to the shape and size of the prostate. The shape can be classified according to the degree of IPP: Grade 1: ≤5 mm; Grade 2: 5-10 mm; and Grade 3: >10 mm, while the size or prostate volume (PV) is classified as follows: (a) ≤20 ml; (b) 20-40 ml; (c) >40 ml. Thus, in robot-assisted laparoscopic prostatectomy there would be nine subtypes: Grade 1a-c, Grade 2a-c, and Grade 3a-c. IPP grade is a better predictor of obstruction than the PV. Grade 1a would be the least obstructive while Grade 3a would be the most obstructive.

It has been shown that IPP is related to bladder outlet obstruction: the greater the IPP then the greater the obstruction and, therefore, the greater the progression of the disease. The severity of BPH can be classified according to the degree of obstruction and symptoms. Significant obstruction can be defined as when there is persistent post-void residual volume >100 ml (inability to empty), or maximum voided volume <100 ml (inability to store). The severity of BPH can be staged according to the presence or absence of bothersome symptoms and significant obstruction:

- Stage I: no significant obstruction and no bothersome symptoms
- Stage II: no significant obstruction but have bothersome symptoms
- Stage III: significant obstruction, irrespective of symptoms
- Stage IV: complications of BPH (e.g. acute or chronic retention, bladder stones)

Decisions on further management can then be made according to the stage and grade (phenotype) of disease in the individual patient. Low-grade, low-stage disease can be watched or counselled, whilst high-grade, high-stage disease needs more aggressive treatment and options for surgery. For patients with bothersome symptoms but no significant obstruction, BPH can be managed with alpha blockers and/or 5-alpha-reductase inhibitors (for patients with PV >30 ml). With this management strategy, the majority of patients (59%) with lower urinary tract symptoms or BPH can be watched, 32% can be managed with medications, and 9% can receive surgery after initial evaluation. This corresponds quite closely with the natural history of a series of patients with prostatism who were followed for 5 years: 84% of patients improved or were stable, 16% deteriorated, and 9% required surgery.

SHORT-TERM PRETREATMENT WITH A DUAL 5α-REDUCTASE INHIBITOR BEFORE BIPOLAR TRANSURETHRAL RESECTION OF THE PROSTATE: EVALUATION OF PROSTATE VASCULARITY AND DECREASED SURGICAL BLOOD LOSS IN LARGE PROSTATES

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The most important cause of lower urinary tract symptoms is benign prostatic enlargement and the histologically confirmed diagnosis of benign prostatic hyperplasia (BPH). BPH displays a prevalence of up to 40% in men in their fifth decade and increases with age.[1] The dual 5α-reductase inhibitor dutasteride blocks the conversion of testosterone into its active form, dihydrotestosterone (DHT), and reduces prostate volume and prostate-specific antigen (PSA) levels while increasing urinary flow parameters. It also decreases the activity of androgen-controlled growth factors responsible for hypertrophy, angiogenesis, and, theoretically, prostatic bleeding during resection.[2] Dutasteride exerts its action specifically on both isotypes of 5α-reductase (Type 1 and Type 2), while finasteride only inhibits Type 2. Dutasteride, in comparison with finasteride, is a 45-fold greater inhibitor of Type 1 and a 2.5-fold greater inhibitor of Type 2 5α-reductase.[3] Bipolar transurethral resection of the prostate (B-TURP) represents an improvement of the traditional TURP, with almost the same efficacy and outcomes but a lower incidence of side-effects (28.6% versus 15.5%).[4]

Assuming that dutasteride exerts an influence on prostatic vascularisation, and assuming B-TURP as a standard procedure for patients affected by BPH, we hypothesised that a short-term pretreatment with dutasteride (0.5 mg daily for 8 weeks) can reduce intra-operative bleeding. A total of 259 patients have been enrolled and randomised to receive either placebo (Group A) or dutasteride (Group B). In particular, we evaluated blood parameters (haemoglobin [Hb] and haematocrit [Ht]), prostate vascularity using vascular endothelial growth factor (VEGF), and microvascular density (MVD) using CD34.

Total testosterone, DHT, PSA, and prostate volume were evaluated and, with the exception of DHT and PSA, there was no statistically significant difference between the two groups. When comparing changes in Hb and Ht between Group A and Group B, before and after B-TURP, there was a statistically significant difference only in cases with a large prostate (≥50 ml). In detail, patients with small prostates (<50 ml) displayed Hb values of 2.41 g/dl (95% confidence interval

[CI]: 1.39-3.43) in Group A and 1.92 g/dl (95% CI: 1.00-2.84) in Group B (difference between groups: 0.49 g/dl, 95% CI: −0.26 to 1.24; p=0.454) (Table 1). A decrease in Ht was observed between Group A (2.22%, 95% CI: 1.77-2.67) and Group B (1.95%, 95% CI: 1.50-2.40) without a statistically significant difference (difference between groups: −0.27%, 95% CI: −0.91-0.38; p=0.411). With regard to large prostates (≥50 ml), the reduction in Hb was significantly lower in Group B (2.05 g/dl, 95% CI: 1.47-2.61) than in Group A (3.86 g/dl, 95% CI: 3.29-4.43) with a treatment effect equal to −1.81 g/dl (95% CI: −2.62 to −1.0; p<0.05); Group B was also characterised by a significantly lower reduction in Ht levels versus Group A (2.64% versus 4.98%, difference between groups: −2.34%, 95% CI: −3.51 to −1.17; p<0.05) (Table 2). The mean MVD and VEGF indicesin prostates of <50 ml were 18.64 (standard deviation [SD]: 1.12) and 2.09 (SD: 0.48), respectively, in Group A, and 17.04 (SD: 0.40) and 1.73 (SD: 0.36), respectively, in Group B, without a statistically significant difference. The mean MVD and VEGF indices in patients with prostates of ≥50 ml were 24.17 (SD: 1.80) and 6.73 (SD: 0.95) in Group A, and 19.49 (SD: 0.44) and 2.44 (SD: 0.49) in Group B (p<0.05 for both indices).

In conclusion, dutasteride treatment was able to reduce operative and peri-operative bleeding only in patients with large prostates (≥50 ml) that underwent B-TURP. Our findings were confirmed by Hb and Ht values reported before and after B-TURP, and reductions in the molecular markers VEGF and CD34 in the dutasteride-treated samples.

Table 1: Blood parameters and vascularisation (prostate size: <50 ml).

	Group A (placebo)	Group B (dutasteride)	p value
Hb before B-TURP, (g/dl) ± SD	14.37±2.12	13.92±2.12	0.48
Hb after B-TURP, (g/dl) ± SD	12.34±1.86	12.19±2.12	0.35
ΔHb ± SD	2.03±0.11	1.73±0.09	
Ht before B-TURP, % ± SD	43.15±3.20	42.48±4.23	0.67
Ht after B-TURP, % ± SD	40.78±3.01	40.15±4.77	0.57
ΔHt ± SD	2.37±0.31	1.83±0.29	
MVD index	18.64±1.12	17.04±0.40	0.09
VEGF index	2.09±0.48	1.73±0.36	0.09

B-TURP: bipolar transurethral resection of the prostate; MVD: microvascular density; VEGF: vascular endothelial growth factor; Hb: haemoglobin; Ht: haematocrit.

Table 2: Blood parameters and vascularisation (prostate size: ≥50 ml).

	Group A (placebo)	Group B (dutasteride)	p value
Hb before B-TURP, (g/dl) ± SD	14.30±2.10	14.01±2.08	0.54
Hb after B-TURP, (g/dl) ± SD	10.50±2.49	11.91±2.15	<0.05
ΔHb ± SD	3.80±0.22	2.10±0.11	
Ht before B-TURP, % ± SD	43.00±3.20	42.66±4.15	0.60
Ht after B-TURP, % ± SD	38.20±3.84	40.16±3.24	<0.05
ΔHt ±SD	4.80±0.67	2.50±0.41	
MVD index	24.17±1.80	19.49±0.44	<0.05
VEGF index	6.73±0.95	2.44±0.49	<0.05

B-TURP: bipolar transurethral resection of the prostate; MVD: microvascular density; VEGF index: vascular endothelial growth factor; Hb: haemoglobin; Ht: haematocrit.

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PEYRONIE'S DISEASE SYMPTOM BOTHER REDUCTION IS RELATED TO PENILE CURVATURE IMPROVEMENT IN RESPONSE TO TREATMENT WITH COLLAGENASE *CLOSTRIDIUM HISTOLYTICUM:* RESULTS FROM TWO LARGE DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED PHASE III STUDIES

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Peyronie's disease (PD) may result in a penile curvature deformity (PCD) that disrupts or prevents sexual intercourse and may result in psychosexual consequences, including significant patient bother.[1] Intralesional injection treatment with collagenase *Clostridium histolyticum* (CCH) has been shown to significantly improve both PCD and symptoms of discomfort as assessed by the Peyronie's Disease Questionnaire PD symptom bother score.[2,3] These measurements were the co-primary efficacy outcome variables for the large, randomised, double-blind, placebo-controlled Phase III studies IMPRESS I and IMPRESS II. The use of CCH was recently approved by the FDA and also by EMA for the treatment of adult men with PD, a palpable plaque, and a curvature deformity of at least 30° at the start of therapy.

The potential association between percentage reduction in PCD and mean improvement in PD symptom bother was investigated among patients treated with CCH in IMPRESS I and II. In this post-hoc analysis, patients with a final PCD ≤45° (n=314) were divided into three groups based on the level of final PCD (Table 1).

All three final PCD groups showed meaningful responses in terms of percentage reduction of PCD (>20%) and mean reduction of PD symptom bother (>2 points) following CCH therapy. The association between greater percentage improvement in PCD and greater improvement in PD symptom bother from baseline to Week 52 (last observation carried forward) was significant ($r=0.30$, $p<0.0001$, $n=314$). The results from this analysis support an association between reductions in PCD and reductions in PD symptom bother.

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Table 1: Change from baseline to Week 52 for the co-primary efficacy outcome variables in the three final penile curvature deformity groups.

PCD at Week 52*	n	Degree of PCD		PD symptom bother	
		Baseline, mean ± SD	Week 52, mean ± SD	Baseline, mean ± SD	Week 52, mean ± SD
≤15°	72	40.0±9.5	9.9±5.1	7.2±3.7	2.1±2.4
>15° to ≤30°	120	45.8±12.1	24.7±4.2	7.0±3.6	3.7±3.1
>30° to ≤45°	122	51.8±13.4	38.2±4.1	7.7±3.2	5.5±4.0

*Last observation carried forward
PCD: penile curvature deformity; PD: Peyronie's disease.

PUSHING THE LIMITS WITH NANOKNIFE®: A PROMISING NEW TECHNOLOGY IN LOCALISED PROSTATE CANCER MANAGEMENT

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INTRODUCTION

In the last few decades, the ever-increasing improvements in cancer detection have allowed urologists to detect prostate cancer (PrC) at earlier stages: currently, in industrialised countries, most diagnosed prostate tumours are small and localised.[1] As a direct consequence, health-related quality of life (QoL) has become a prominent factor in treatment decision-making for localised PrC. Indeed, approaches such as radical prostatectomy (RP) and external beam therapy have been associated with significantly impaired urinary, bowel, and sexual functions,[2-4] and some authors might consider these options to be 'excess treatments'.[5] While there is continuing uncertainty regarding the superiority of one therapeutic modality over another, what has become certain is that maintaining QoL, especially in younger patients, is now playing a central role, thus generating interest in less radical options.

In recent years, focal therapy has emerged as a 'middle ground' option between active surveillance and radical modalities in patients with low-to-intermediate-risk PrC. Indeed, focal therapy has the potential to address the needs stated earlier and offer minimally invasive options to optimise risk stratification at diagnosis. These options include cryotherapy,[5,6] which is currently considered as an alternative option by the European Association of Urology (EAU) and American Urological Association (AUA) guidelines.[7-9] Other focal therapy options comprise experimental modalities such as high-intensity focused ultrasound (HIFU),[10-12] photodynamic therapy,[13,14] brachytherapy, irreversible electroporation (IRE), and focal laser ablation.[15,16] While the clinical data to date has confirmed the potential for these emerging techniques to provide higher benefit-to-risk ratio in localised PrC, most of these options are thermal options using energy to target cancerous cells, thus possibly generating tissue damage.

However, one of the upcoming techniques is non-thermal: IRE. IRE is a non-thermal modality that could very well have the potential to provide improved perioperative and long-term functional outcomes and reduced treatment-associated morbidity without compromising on the oncological results. This paper will provide an overview of the promising perspectives offered by IRE through a discussion with two key experts in the field, Prof Jean de la Rosette (Amsterdam, the Netherlands) and Prof Mark Emberton (London, United Kingdom); both are at the forefront of IRE clinical research, as they are the principal investigators for the Clinical Research Office of the Endourological Society (CROES) Registry and the Novel Endovascular Access Trial (NEAT), respectively.

Interview with Prof Jean de la Rosette

Prof Jean de la Rosette is a Professor and Chairman of the Department of Urology at AMC University Hospital in Amsterdam, the Netherlands.

Prof de la Rosette was chairman of the European Association of Urology (EAU) working party on benign prostatic hyperplasia guidelines from 1996 to 2004. He is a member of various urological societies: e.g. the Endourological Society, the American Urological Association (AUA), the European Association of Urology (EAU), and the Société Internationale d'Urologie (SIU).

Prof de la Rosette has authored over 300 peer-reviewed publications and many book chapters. He is also on the editorial board of the Journal of Endourology and European Urology.

Prof Jean de la Rosette is the Coordinating Investigator and Chairman of the CROES Registry on IRE for the ablation of PrC with use of the NanoKnife® device. CROES is an official organisation within the Endourological Society responsible for organising, structuring, and favouring a global network on endourological research.

The CROES registry is a multicentre, international, observational study aiming to evaluate the treatment of PrC in terms of recurrence, functional outcomes, and safety (Clinicaltrials.gov identifier: NCT02255890).

The primary objective of the registry is to assess the recurrence of PrC at 1 and 5 years, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline. Secondary study objectives will aim to establish which indications lead to treatment with IRE NanoKnife setting, and safety assessments measured by the number of complications and adverse events (AEs).

Inclusion criteria are as follows:
- *patient is diagnosed with histologically confirmed PrC*
- *patient is scheduled for IRE NanoKnife*
- *patient has signed informed consent form*

We interviewed Prof de la Rosette to discuss the increased interest in effective focal therapies for the treatment of low-risk PrC, the CROES Registry on IRE, and the NanoKnife system's potential (interview conducted on 4th March 2015).

Can you tell us more about the inception of the IRE CROES Registry? How did it come to be?

From a urological point of view, ablative treatment modalities are receiving increasing interest over resection or radiation therapy (RT) of the whole gland.

AngioDynamics holds a special interest in technology that can be applied in various oncological conditions and wants to position NanoKnife according to the highest standard possible.

To this effect, certain steps should be followed, namely Phase I/II studies to study the efficacy of the treatment, randomised clinical trials (RCTs) to study one versus another treatment option, and registry studies to determine the real-life position of such a therapy.

First, we concluded a Phase I/II study in a subgroup of 16 patients within a fully institutional review board (IRB)-approved setting (Clinicaltrials.gov identifier: NCT01790451).[17]

We offered patients who needed RP for a somewhat more extended (but still localised) disease the possibility to participate in a project where they would receive ablative treatment according to a fixed protocol, and then this would be followed by RP 4 weeks later.

The interesting part of this study was that in the 4 weeks follow-up for IRE treatment, we could evaluate the morbidity that the treatment could cause, and it was minimal. We had a special interest in voiding function disturbances and again these were minimal or non-existent. We also looked into patients' QoL related to the treatment, such as pain (minimal, only some discomfort

during the first days) and sexual functions (erections and ejaculations), which were not disturbed in the 16 patients.

Based on this strong foundation that QoL was not affected, we endeavoured to conduct efficacy assessments, meaning: *"If I treat a certain area to a protocol, is all the tumour which is within the area ablated: do we have skipped lesions?"* And again, we confirmed in all 16 patients that the fully treated area was completely ablated and that there was no vital tissue left.

Also of importance was that we wanted to know if we could properly monitor the effect of the treatment with an imaging modality 4 weeks, 6 weeks, 3 months, or even 1 year after the treatment. In the first few weeks, we were able to demonstrate that both magnetic resonance imaging (MRI) and multiparametric ultrasound could give us the information.

With the results of this Phase I/II study in mind, we felt that there was a strong argument to proceed to an RCT and also to continue with a registry: both were actually initiated more or less at the same time.

As the CROES was founded to support research in the field of endourology, in this registry all the research is co-ordinated by an independent society.

For patients, what would be the rationale to take part in the registry versus the RCT?

Some patients might feel that ablative treatment is attractive but they do not wish to participate in an RCT or they prefer to do it within a registry. The argument is that they are not interested in extended questionnaires to fill out, nor are they interested in coming to regular and fixed assessments.

The registry can also include patients who would like to have ablative therapy but would not be cleared to take part in an RCT.

An RCT is conducted in a very select patient population. In reality, a wide range of different patients are treated.

Let us say that within an RCT, erectile dysfunction is an outcome parameter: investigators have to exclude patients who have pre-existing potency problems. As the registry is a real-life data study, we are following up on multiple QoL parameters.

In addition, in a study protocol, elderly and more fragile patients may be excluded. However, patients may also ask if they can be candidates for such a treatment. Within a registry, we can properly document these subgroups and their additional benefits. We made this registry open on a global scale, for every centre that has access to IRE.

For such centres, what is the advantage for them to share their data?

Well there are multiple [advantages]: first of all, the data are shared with an independent society, which means a high level of quality control (QC) can be expected. Clinicians can compare the outcomes of their data set with data from the whole registry. We have learned from other technologies that have been introduced that this is important: for example, for brachytherapy with seed implant, the QC in the beginning was not optimal and there was a centre in the USA that performed hundreds of implants but these were not set optimally. If at an early stage a centre recognises that maybe the treatment is not optimal or that some complications arise, they can discuss the indications and maybe also receive our support to improve their outcomes.

The other advantage is that the centres get a certificate to prove that they are following the appropriate protocol. Such a certificate confirms that the institute is offering patients the highest quality of care, maybe not in a randomised study but within a registry and sharing, on a global basis, the data and outcomes.

I am very happy with the protocols and projects that we have embarked on to determine what the exact position of this technology is for the treatment of PrC. I am also glad that both endourological societies strongly support these projects in addition to AngioDynamics, even if these studies are independent.

Since the main unmet needs for resection are associated with impaired QoL and functional outcomes, do you feel that the registry will provide a population-based analysis that will help differentiate IRE in terms of functional outcomes, QoL, and the range of issues that patients are very keen to see addressed in the coming years?

With respect to many of the questions that are put forward, at this stage this would be speculation.

Of course, patients nowadays are more concerned about their QoL parameters than some years ago. Trying to preserve a good oncological outcome is still paramount, but maintaining QoL has become essential and is playing a central role. Ten years ago, patients were more concerned about the oncological outcomes ("Am I cured?"). At the moment, the questions are very specific: "I want to maintain my quality of life."

Patients have become increasingly aware that they have friends or relatives that have had treatment where the morbidity is playing a more prominent role now and they are not questioning whether they were cured, but rather if they were cured at a very high price.

In the end, patients need to have data that support this. I know that hundreds of patients have already been treated for PrC with NanoKnife, but if you look at the number of publications these are limited, which means the cases were not properly documented.

If that had been the case, they could have been in support of already having this treatment properly recognised and positioned within guidelines.

How many patients have been included in the registry so far, and how many do you expect to recruit?

We started in January 2015, so for now we have a handful of patients.

At present we have 20 international sites that are willing to recruit or to include data. If each centre recruits 30 cases we will have 600 patients in a year. But I am confident that we will have more centres throughout the world participating in this venture. So in 5 years we will have a minimum of 3,000 patients: that is a powerful data set.

Besides the Phase I/II study and the CROES registry, can you tell us more about the RCT on NanoKnife you mentioned earlier?

In the RCT *(Clinicaltrials.gov identifier: NCT01835977),* we want to study a subgroup of patients who have more limited disease in one lobe of the prostatic gland, and if we can, again safely and with minimal morbidity, treat that disease by targeting only the lesion, randomised against a more extended treatment.

This study has been initiated: IRB approval was recently granted at our department (Department of Urology, AMC University Hospital in Amsterdam, the Netherlands), and in Europe, seven centres are now preparing their IRB approval to get started as well.

Do you think NanoKnife has the potential to become part of salvage therapy strategies following RT failure?

At this point it would be pure speculation to say so. One-third of all patients who receive external beam RT show a failure after some time of follow-up: all possible additional treatments in this case harbour a risk. Ablative treatment, including IRE, in the case where a lesion is on the peripheral zone closer to the rectum, can cause significant harm with the development of a fistula.

Salvage therapy sounds attractive but we need to instruct our patients very carefully and also carefully document these data to know how far we can push technology and its applications. I would say we should first document the real possibilities and then go for the next steps instead of jumping on this group of RT failures.

Do you think NanoKnife could be more effective to healthcare payers as a less radical approach given its safety profile and associated costs?

Let us say in the ideal case scenario a patient comes to the hospital to receive IRE and leaves the same day or the next day, with no voiding complaints, no incontinence, and no erectile dysfunction. The only thing required is an MRI to confirm that the entire tumour has been eradicated and a close follow-up to check for recurrences. That is the drawback: the prostate is still there and the patient might develop a new prostatic cancer as it is related to the biological behaviour of the prostate.

However, you are right, QoL is important: the patient does not need to take oral medication to have improvement of sexual function, there is no need for physiotherapy for incontinence or for diapers to protect clothes against urine loss. Patients do not feel embarrassed or unhappy. A lot of additional costs are erased with this technology and this day-care case scenario.

If everything is put into balance, I think it would be in favour of IRE, but again this is pure speculation that needs to be confirmed.

Having said that, is it too soon to conduct health-economic studies of IRE?

Health economic studies warrant specific study design.

In the registry and the RCT cited above, the centres involved will include the economic data. But health economics is not an easy issue to assess: costs highly depend on the country as well as reimbursement parameters with respect to the alternatives.

Do you feel that some of the resistance to focal therapy will finally be overcome soon?

Any alternative will be embraced not only by the patient but also by the payers, if there is a significant benefit not only for patients but also in reducing costs. Once new treatment modalities are discussed in the guidelines, patients and practitioners believe in their validity. However, the treatment will still need to be tailored according to the clinical setting and patient characteristics.

Interview with Prof Mark Emberton

Prof Mark Emberton is a urologist and Professor of Interventional Oncology. He directs the Division of Surgery and Interventional Science at University College London (London, United Kingdom).

Within this centre of excellence, he is at the forefront of clinical research in urology and his principal interests lie in advancing research on the diagnosis (novel imaging techniques) and management (novel minimally invasive techniques) of prostate cancer.

He lectures widely and has authored over 300 articles in peer-reviewed journals.

Prof Emberton is the main investigator for the single-centre, prospective, development Stage IIa NanoKnife Electroporation Ablation Trial (NEAT, Clinicaltrials.gov identifier, NCT01726894), which is currently ongoing. The recruitment phase (20 men with localised PrC) was completed in 2014 and first results are expected in August 2015.

We interviewed Prof Emberton to discuss the increased interest in IRE for the treatment of low-risk PrC and the NanoKnife system's potential (interview conducted on 24th February 2015).

To you, what distinguishes IRE from other focal therapies?

The main difference between IRE and the other focal therapies is that it is non-thermal, and this attribute makes it unique amongst focal therapies: this is important, as heat is unpredictable in the body because there are mechanisms to redistribute heat in tissues.

I think cryotherapy is also difficult to predict because of the different vascularity among tissues and therefore the different amount of ice that is required. Also, it is difficult to control the outer limits of the ice bowl.

As IRE is non-thermal, the conductive properties of the tissue seem to be much more homogenous than the properties associated with the distribution of heat.

Moreover, it can also be used when the prostate is calcified (in which HIFU is contraindicated because the energy would be reflected and redistributed). These attributes of IRE technology certainly make it a distinct treatment modality.

So far, the clinical and safety data of focal IRE in PrC are encouraging. Could you update us on the status of NEAT?

We do not have any results yet and we will analyse the primary outcome once all the patients have completed the study. One of the most interesting things about the trial is the rate at which we recruited. Early PrC studies mostly, in fact exclusively, have failed to recruit in the past with about 10-15 studies closing early due to failure to recruit.

For the NEAT study, patients were fighting to be included because there were only 20 slots.

How do you explain this?

I think it is due to two reasons. First, this trial gives patients the opportunity to benefit from tissue-preserving therapy, as focal treatment for PrC is associated with much better functional outcomes. We think the morbidity aspect played a role in this fast recruitment. Patients very much respond to the idea of improved QoL.

Secondly, men liked the attributes of the technology: it is a quick, day-care procedure and it is a non-thermal technique.

You were part of a consensus meeting in June 2013 to discuss focal therapy.[18] Further to this meeting, do you envision focal therapy to become a standard first-line treatment in selected men with localised PrC (low-risk and low-risk shifting to high-risk) in the coming years?

It is becoming just that in our centre, for the treatment for men with focal moderate-to-high-risk disease.

Do you feel that some of the resistance to focal therapy seen in the field will finally be overcome, just as radical mastectomy was slowly replaced by breast-conserving surgery in early-stage breast cancer?

I think now there is a certain animosity and scepticism about the lack of long-term data, and possibly fear of new technologies that are evolving and are difficult to master.

Could this scepticism be due to the lack of large-scale trials difficult to implement in PrC?

Yes, but this did not stop some novel technologies before: most developed PrC modalities were developed without RCTs, such as RP, laparoscopic prostatectomy, and active surveillance. IRE is a fairly easy-to-do procedure: it would allow physicians to perform focal therapy in their own practice, without a long learning curve. But I agree, we do need to conduct randomised clinical trials for IRE in order to further establish this technique.

Do you think that IRE has the potential to become part of salvage therapy strategies following RT failure?

Very much so. I have used it on a couple of occasions, and with good results. This was conducted in difficult-to-treat patients, mainly after brachytherapy failure.

Could you please describe one case?

In one patient, brachytherapy failed and was followed by external beam radiotherapy, but the patient had a recurrence in the anterior part of the left side of his prostate.

I used IRE to treat him; as his prostate was quite small, cryoablation would have been difficult. There was also quite a bit of calcification in the prostate, so HIFU would have been difficult or impossible.

We conducted IRE with four needles around the lesion and obtained very good confluent necrosis of the lesion with a nice margin. He was treated without any observed toxicity. The patient is now stable at 1 year follow-up, without any sign of disease recurrence.

Could IRE be more cost-effective to healthcare payers as a less radical approach and associated clinical outcomes and safety profile?

It could be as it is a quick day-care treatment with less infrastructure required as compared with RP, radiotherapy, or proton treatment.

IRREVERSIBLE ELECTROPORATION: MECHANISM OF ACTION

IRE is a novel soft tissue ablation technique using non-thermal energy to create innumerable permanent nanopores in the cell membrane to disrupt cellular homeostasis (Figure 1). Disruption of cellular homeostasis triggers complete tissue death by means of apoptosis or 'apoptosis-mimetic' necrosis.[19-22] Electroporation works by providing a certain electrical field that has the ability to change the electrochemical potential across cell membranes, thus inducing instabilities in the polarised lipid bilayer and creating nanopores in the cell membrane. As a function of the field amplitude and duration, the permeabilisation can be reversible or irreversible.[23] With a pulse length of approximately 100 µs and an electric field of approximately 1 kV/cm (Figure 2),[23] the short and strong field produced by IRE generates apoptotic cell death, which comprises immune-mediated cell death and phagocytosis (macrophages aiding in clearing cell debris) leading

to tissue regeneration as a natural course of the cell cycle.[19,21,24]

Contrary to thermal ablation, which causes heat-induced protein denaturation, non-thermal necrosis generates an energy delivery producing transient tissue temperatures lower than 50°C with no Joule heating.[19,21] Thus, it has the ability to preserve critical structures within the IRE-ablated zone, affecting only the cell membrane and no other structure within the tissue, such as the urethra, the extracellular matrix, larger blood vessels (and blood flow), or nerves (Figure 3).[19,25-28]

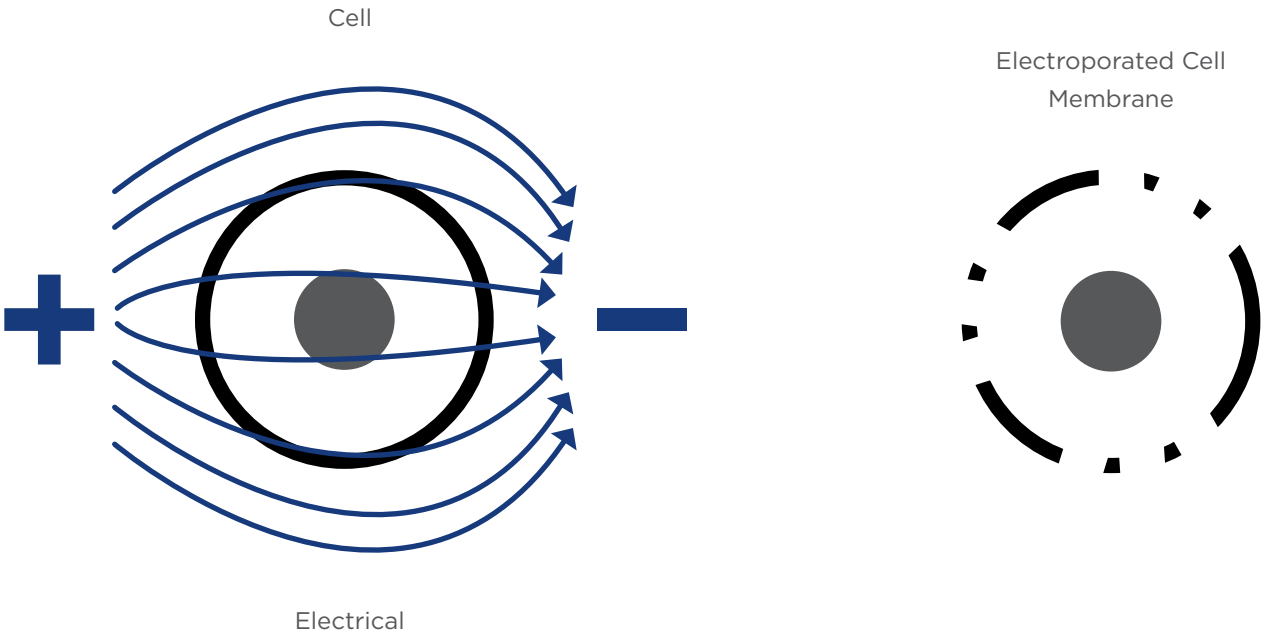

Figure 1: Irreversible electroporation: mechanism of action.
(AngioDynamics, data on file)

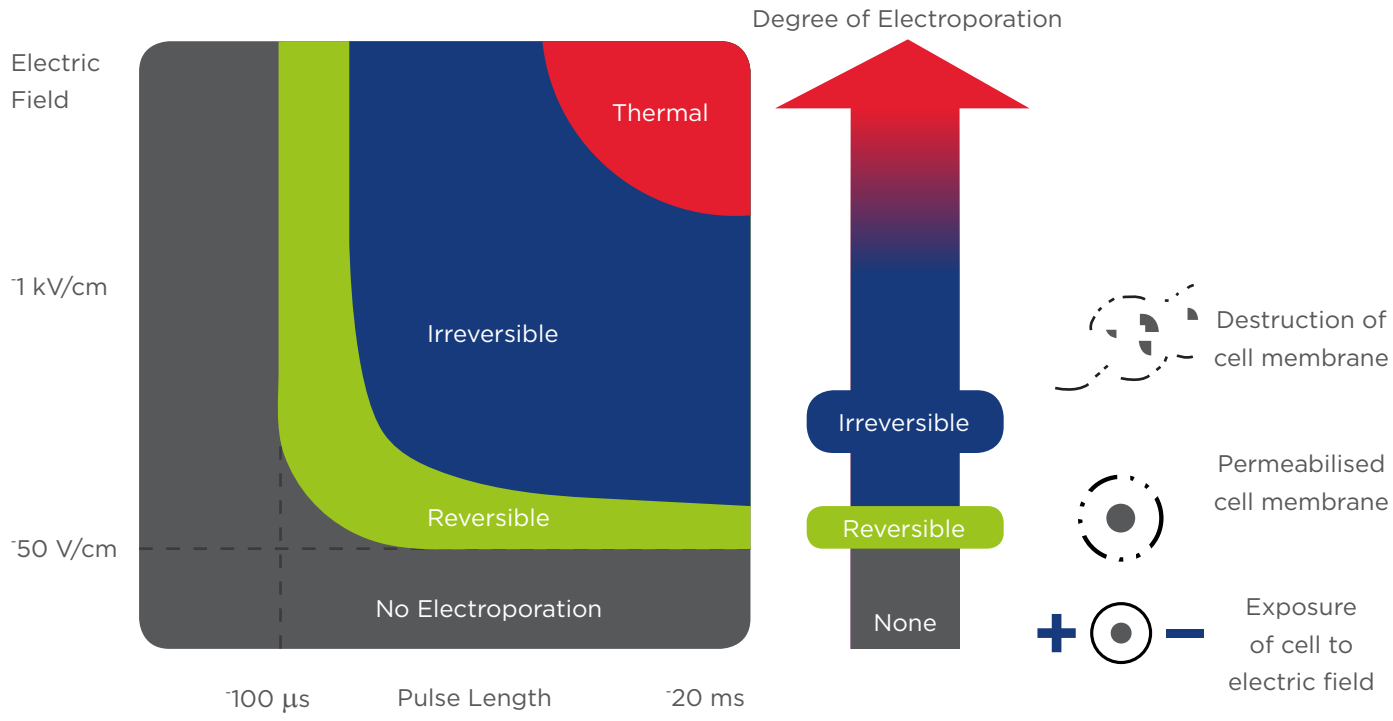

Figure 2: Electric field settings for reversible and irreversible electroporation.
Adapted from Bower et al.[40]

Moreover, while conventional thermal ablation techniques can be hindered by the 'heat sink effect' phenomenon, as perivascular tissues are not completely ablated and lead to incomplete ablation of the tumour, IRE can cause complete tissue death even when the ablation zone is close to a large vessel.[24] IRE produces an extremely sharp, well-demarcated, and predictable ablation area, and the transition between healthy and ablated tissue can be observed on a cellular level, thus contrasting with that observed with other ablative modalities.[20,25]

THE NANOKNIFE SYSTEM

The NanoKnife® system (AngioDynamics, Queensbury, New York, USA) is CE marked for cell membrane electroporation and consists of a NanoKnife generator (Figure 4) and up to six single-use disposable monopolar electrodes, comprising one activator radiofrequency identification (RFID) monopolar electrode (Figure 5), and up to five RFID monopolar electrodes (Figure 6). The electrodes are placed under computed tomography or ultrasound guidance. An electrocardiogram synchroniser (AccuSync® Synchronization Device; Figure 7) completes the system to limit the risk of ventricular tachycardia.[29]

PROCEDURE

The procedure is a 1-day, outpatient procedure: after waking up from general anaesthesia, the patient can return home the same evening or the next morning. A typical IRE procedure on a solid tumour uses about 90 100-microsecond pulses delivered by a certain number of needles (according to the pre-defined treatment strategy) that are positioned on the margin of the treated area, usually with ultrasound guidance.

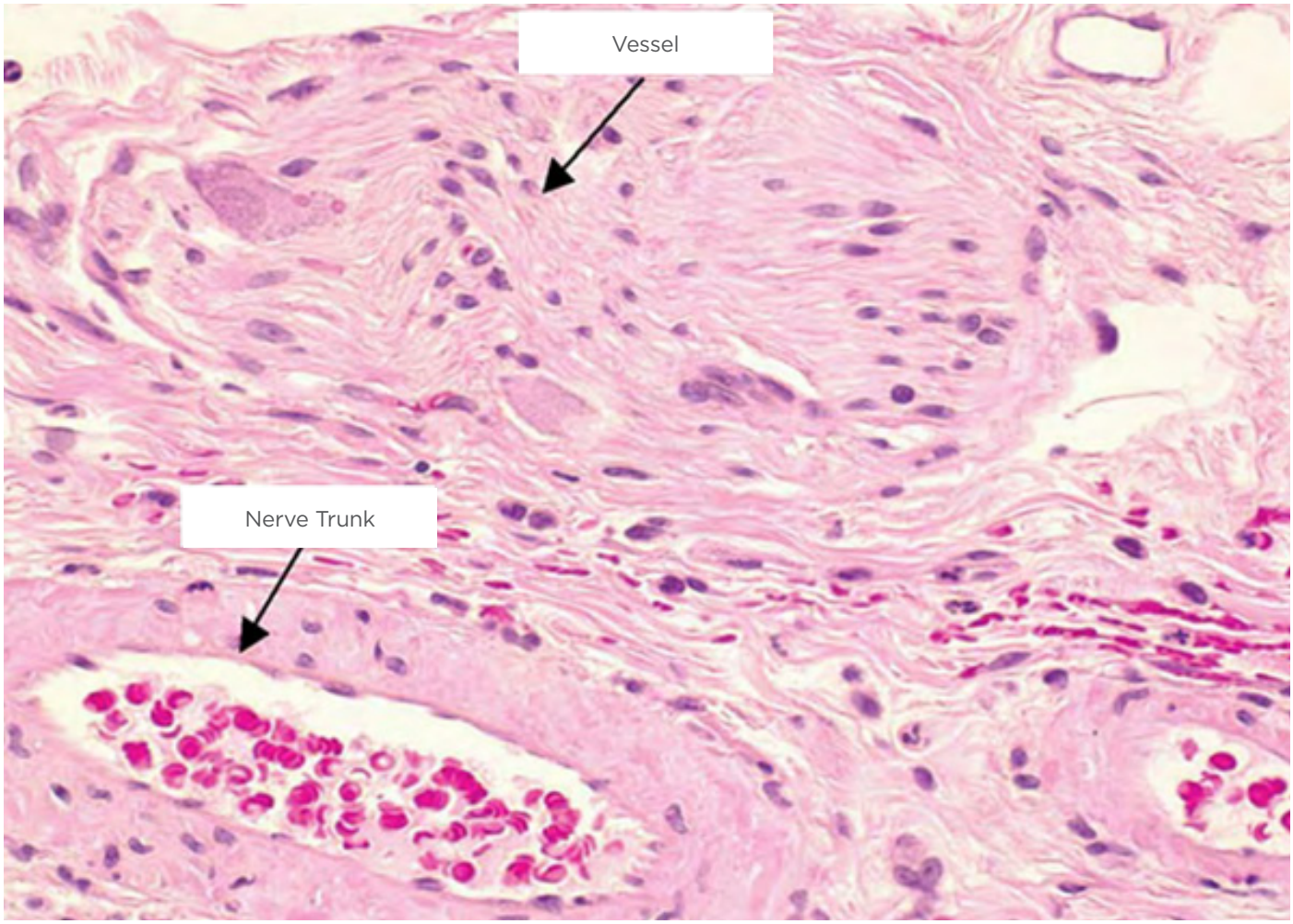

Figure 3: Irreversible electroporation (IRE) in the prostate: photomicrograph of a neurovascular bundle post-IRE.
Adapted from Onik et al.[20]

Figure 4: The NanoKnife® generator.
(AngioDynamics, data on file)

Figure 5: NanoKnife® activator RFID monopolar electrode.
RFID: radiofrequency identification.
(AngioDynamics, data on file)

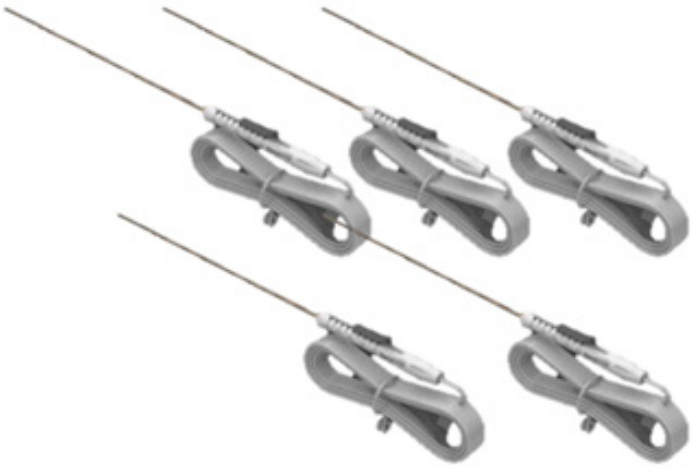

Figure 6: NanoKnife® RFID monopolar electrode (up to 5).
RFID: radiofrequency identification.
(AngioDynamics, data on file)

Figure 7: The AccuSync® synchronisation device.
(AngioDynamics, data on file)

Within three or four overlapping ablations, total IRE treatment time is under 5 minutes, which may correlate with reduced anaesthesia time, reduced post-ablation pain, decreased ablation-related complications, as well as decreased overall cost of ablation treatment, and it may provide an opportunity for treatment of multiple lesions or multiple treatments of a single lesion in one session.[19] MRI may be used pre and post-procedure to evaluate the evolution of the lesion.

Table 1: Available clinical data on IRE in localised PrC.

Study	Key findings
Pilot safety study[30]	**Objectives:** The primary objective of the study was to test the procedural and short-term safety of the device to ablate localised microfocal, low-grade PrC. A secondary objective was to evaluate the effectiveness of the treatment and its impact on quality of life of our patients. **Population:** 11 patients with PrC were enrolled after ethical committee approval and informed consent. **Eligibility criteria:** unilateral PrC on template-guided perineal biopsies (1.37 cores per cc), prostate specific antigen (PSA) <10 ng/ml, Gleason score <7, Stage cT1c/T2a. Mean pre-operative PSA was 6.43 ng/ml, mean prostate volume on transrectal ultrasound (TRUS) was 62.3 cc. Stage: cT1c=10 and cT2a=1. **Methods:** The procedure was performed under general anaesthesia using the brachytherapy grid to reach the same area where PrC was detected at biopsy. The mean number of needles used to treat the tumour area was 6.3 (range: 4-10). Mean treatment time was 7.8 min (range: 2-18 min). **Results:** No major complications occurred during the procedure. Hospital stay was 1 day for all patients. Prostate biopsy of the treated area was performed after 1 month using local anaesthesia. No major complications were observed after 14, 30, 90, and 180 days, and 19.2 months. A total of 1/11 patients (9%) had acute urinary retention and 3/11 patients (27%) had transient urge incontinence. The mean PSA after 30, 90, and 180 days, and 19.2 months went down to 3.5, 2.9, 3.3, and 3.12 ng/ml, respectively. The continence rate was 100%. The pathological report after 30 days was negative in 8/11 patients (73%). Coagulative necrosis, granulomatosis, fibrosis, and haemosiderosis were commonly reported. Persistent adenocarcinoma was present in 3/11 patients (27%) (1, 1, and 2 foci), respectively. One patient received RP, one was re-treated, and one is awaiting re-treatment. **Conclusion:** IRE is a safe procedure for focal therapy in localised low-risk PrC. It is relatively simple, minimally invasive, and effective. Further larger studies with longer follow-up are needed to confirm these preliminary results.
Pilot study[31]	**Objective:** To explore the first human use of IRE in this setting. **Population:** 16 patients (age range: 40-78) with localised PrC were treated with IRE. **Methods:** Patients were considered for cancer-targeted IRE ablation if (based on TRUS biopsies) their cancer was localised and the maintenance of potency and/or continence was a major concern of the patient. A total of 18 gauge IRE electrodes were placed under TRUS guidance percutaneously through the perineum. IRE probes were placed to cover the known area of cancer location based on the patients mapping biopsy. Four probes were placed in a roughly square array, 1-1.5 cm apart, with the known area of cancer in the centre of the array. At 3 weeks post-treatment additional transperineal ultrasound-guided biopsies were conducted in the previously known cancer loci and the immediate surrounding areas. **Main results:** Post-operative biopsies taken from the area of previously known cancer in 15 patients showed no evidence of cancer. There was one patient with a negligible PSA who refused a post-operative biopsy and one in whom a micro focus of Gleason score 6 cancer was found outside the treated area. This patient was successfully retreated with focal cryosurgery. In addition, there was no evidence for any viable glandular tissue in the biopsy specimens. Haematoxylin and eosin staining showed all epithelial elements gone. There were occasional areas with ghosts of glandular structures without viable cells present. Vascular elements were patent and intact nerve bundles with viable ganglion cells within them were noted, surrounded by necrotic tissue and fibrotic tissue. **Conclusion:** IRE is a new non-thermal ablation modality with significant advantages over heat or cold-based tumour destruction. Its ability to spare nerves and vessels apparently results in minimal effect on potency, making it particularly suited to the focal therapy of PrC.
Prospective study[32]	**Objective:** To evaluate the safety and clinical feasibility of focal IRE of the prostate. **Population:** A total of 34 patients undergoing focal IRE for localised PrC in two centres. **Methods:** Eligibility was assessed by multi-parametric MRI (mp-MRI) and targeted and/or template biopsy. IRE was delivered under TRUS guidance with two to six electrodes positioned transperineally within the cancer lesion. **Main Results:** Overall, 34 patients with a mean age of 65 years and a median PSA of 6.1 ng/ml were included. 9 (26%), 24 (71%), and 1 (3%) had low, intermediate, and high-risk disease, respectively. From a functional point of view, 100% (24/24) were continent and potency was preserved in 95% (19/20) of patients who were potent before treatment. The volume of ablation was a median 12 ml with a median PSA after 6 months of 3.4 ng/ml. Mp-MRI showed suspicious residual disease in 6 patients (25%), of whom 4 (17%) underwent another form of local treatment. **Safety:** After a median follow-up of 6 months (range: 1-24), 12 Grade 1 and 10 Grade 2 complications occurred. No patient had Grade ≥3 complication. **Conclusion:** Focal IRE has a low toxicity profile with encouraging genito-urinary functional outcomes. Further prospective development studies are needed to confirm the functional outcomes and to explore the oncological potential.

Table 2: Ongoing/upcoming clinical studies on IRE in localised PrC.

Ongoing/upcoming study	Study design, population, and outcomes
CROES Phase I study[17] (ClinicalTrials.gov Identifier: NCT01790451)	**Study design:** Multicentre prospective human pilot Phase I study. **Population:** 16 patients with PrC who are scheduled for RP will undergo an IRE procedure, approximately 30 days prior to the surgery. **Data collection:** Data of AEs, side-effects, functional outcomes, pain, and quality of life (QoL) will be collected and patients will be controlled at 1 and 2 weeks post-IRE, and 1 day pre-prostatectomy and post-prostatectomy. Prior to the IRE procedure and the RP, all patients will undergo an mp-MRI and contrast-enhanced ultrasound (CEUS) of the prostate. **Outcomes:** The efficacy of ablation will be determined by whole-mount histopathological examination, which will be correlated with the imaging of the ablation zone.
NEAT[33] (ClinicalTrials.gov Identifier: NCT01726894)	**Study design:** Single-centre prospective IIa study. **Population:** 20 men who have MRI-visible disease localised in the anterior part of the prostate will be recruited. Inclusion criteria include PSA ≤15 ng/ml, Gleason score ≤4 + 3, Stage T2N0M0, and absence of clinically significant disease outside the treatment area. **Data collection:** Treatment delivery will be changed in an adaptive, iterative manner so as to allow optimisation of the IRE protocol. After focal IRE, men will be followed during 12 months using validated patient-reported outcome measures (International Prostate Symptom Score [IPSS], International Index of Erectile Function [IIEF]-15, UCLA EPIC, EuroQoL 5D, Functional Assessment of Cancer Therapy-Prostate [FACT-P], Memorial Anxiety Scale for Prostate Cancer). Early disease control will be evaluated by multi-parametric and targeted transperineal biopsy of the treated area at 6 months. **Outcomes:** NEAT will assess the early functional and disease-control outcome of focal IRE using an adaptive design. **Estimated Primary Outcome Completion Date:** August 2015.
Phase II CROES Clinical Trial[34] (ClinicalTrials.gov Identifier: NCT01835977)	**Study design:** Phase II clinical trial. **Population:** Six European centres will randomise 200 patients into focal ablation versus extended focal ablation with tumour in one prostate lobe. The CROES will conduct a study titled *'Multicenter Randomized Two-Arm Intervention Study Evaluating Irreversible Electroporation for the Ablation of Localized Unilateral PrC.'* **Outcomes:** With this Phase II clinical trial, the investigators want to compare focal ablation versus extended focal ablation with IRE in patients with unilateral low-to-intermediate-risk PrC. Primary objectives are to determine if focal ablation has fewer side-effects than whole-gland ablations measured by IPSS, IIEF, time of catheter a demeure, Visual Analog Scale pain scores, and length of hospital stay. The secondary objective is to determine the oncological outcome of IRE focal ablation in comparison with extended focal ablation. This will be measured by standardised transrectal biopsies and mp-MRI findings in follow-up. Furthermore, the objective is to determine if there is a difference in the QoL between patients who are treated with focal ablation and those treated with extended focal ablation measured by FACT-P. **Estimated Primary Outcome Completion Date:** February 2018.
CROES Registry of Irreversible Electroporation for the Ablation of PrC With Use of NanoKnife Device[35] (ClinicalTrials.gov Identifier: NCT02255890)	**Study design:** Multicentre international registry (observational study). **Objectives:** The aim of this registry is to assess the recurrence of PrC at 1 and 5 years, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline. Secondary objectives are to establish which indications lead to treatment with IRE setting, and safety assessment measured by number of complications and AEs. **Target follow-up duration:** 5 years.

WHAT'S NEW ON FOCAL THERAPY FOR PROSTATE CANCER?

Highlights from the European Association of Urology Annual Meeting (Madrid, 20th-24th March 2015)

At EAU, Prof Emberton presented an interesting webcast, *'Evolving concept and technique in focal therapy, reality or myth?',* in which he reviewed the advantages of targeted biopsy for PrC detection and diagnosis versus a systematic approach, before discussing the need for tissue-preserving modalities in localised PrC.

Prof Emberton also examined the concept of treating the index lesion (which is thought to be responsible for disease progression) in multifocal localised PrC with focal ablation.[36] He welcomed the emergence of focal therapy as a legitimate new class of therapy, which now commends legitimacy and will most likely help refine the risk stratification rationales and treatment strategies.

In Vivo Data on a Novel Thermal Ablation Technique

A novel thermal ablation technique, convective water vapour therapy (steam), was explored in a prospective multicentre study: 14 patients underwent concomitant transperineal, ultrasound-guided vapour treatment followed by RP under the same anaesthetic.[37] Thermal ablation was clearly identified in all pathologic specimens. The peripheral and/or transition zones could be selectively targeted. Needle placement, vapour injections, and treated areas could be clearly visualised by real-time ultrasound monitoring. Extraprostatic tissue injury was not observed.

Follow-Up After Focal Therapy

The very interesting and crucial question of follow-up after focal therapy was addressed with the results of an international multidisciplinary (76 participants: 70% urologists, 28% radiologists, and 2% biomedical engineers) consensus questionnaire.[38] Indeed, since focal therapy predominantly preserves the prostate, the possibility of developing a new PrC remains, especially in elderly patients with risk factors. This Delphi consensus group concluded that in order to include focal therapy as a standard of care treatment, standardised follow-up is essential. The follow-up after focal therapy should be a minimum of 5 years and should include mp-MRI, prostate biopsies, and assessment of erectile function, QoL, urinary symptoms, and incontinence. All data should ideally be pooled in a common global database to provide important and consistent outcome data.

Moreover, van den Bos et al. presented the results of a prospective study conducted on 16 patients scheduled for RP and in which IRE procedures were performed approximately 4 weeks before surgery.[39] The aim of the study was to determine the most feasible imaging modality for accurate visualisation of the IRE ablation zone. Prior to and 4 weeks after the IRE procedure, imaging of the prostate was performed by ultrasound, CEUS, and mp-MRI. Grey-scale ultrasound and Tesla (T)2-weighed MRI were deemed insufficient to assess IRE ablation volume, while CEUS and dynamic contrast enhanced MRI were determined as the most feasible imaging modalities to visualise the IRE ablation zone, and closely matched the histopathology shape and volume of the ablation zones.

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CHEMOTHERAPY AND NEW DRUGS IN PROSTATE CANCER

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INTRODUCTION

Prostate cancer (PrC) is the fourth most common cancer (for both sexes combined) and the second most common cancer in men (accounting for 15% of all new male cancer cases), with a worldwide incidence of approximately 1,111,200, a 5-year prevalence of 3,924,000, and a mortality incidence of 307,000 for the year 2012.[1] Since the 1990s, the increasing use of prostate-specific antigen (PSA) testing has had a significant influence on incidence rates, much more so than on mortality rates.[1] As diagnosis can be established very early in the disease, most cases of PrC are treated at a localised stage with very good 10-year relative survival and progression-free survival (PFS) rates.

However, some men might develop advanced or metastatic disease at diagnosis or following initial treatment, requiring the use of systemic therapy including chemotherapy in some cases. According to the Surveillance, Epidemiology, and End Results Program (SEER) database for the period 2004-2010, 81% of PrC patients in the USA were diagnosed with local disease, and only 12% and 4% presented with regional and metastatic disease at diagnosis, respectively.[2] Advances in clinical research have led to the development of several strategies to manage advanced PrC. This review aims to summarise the current standard of care (SoC) for chemotherapy use in castration-resistant prostate cancer (CRPC) or hormone-sensitive prostate cancer, in light of the available new hormonal treatments.

CLINICAL SETTINGS REQUIRING CHEMOTHERAPY USE IN PROSTATE CANCER

As opposed to many other malignancies, cytotoxic chemotherapy (CC) in PrC has no place as a neoadjuvant treatment modality in 2015. However, within the last two decades, taxane-based combination regimens have emerged as significant therapeutic options in metastatic CRPC (mCRPC). Chemotherapy in PrC primarily includes docetaxel and cabazitaxel, both taxanes. In 2015, during the last European Association of Urology (EAU) meeting in Madrid, the EAU published the latest version of their guidelines for the management of PrC, based on a systematic review of all the available clinical evidence to date.[3] The current guidelines mainly reserve the use of docetaxel chemotherapy for patients with mCRPC, as first-line and second-line treatment modalities. The American Urology Association (AUA) also only recommended docetaxel-based chemotherapy but mainly in symptomatic mCRPC.[4,5] Mitoxantrone was recommended by the AUA in mCRPC patients with good performance status and who were not eligible for docetaxel therapy, but mitoxantrone only confers a quality of life (QoL) benefit and no survival benefit.

HIGH-RISK/LOCALLY ADVANCED PROSTATE CANCER

While androgen deprivation therapy (ADT) combined with radiotherapy provides significant and sustained positive clinical outcomes in men with advanced disease, most patients will develop resistances to hormone therapy over time, as is the case with most hormone-dependant malignancies.

To date, only two studies have evaluated the use of chemotherapy as an adjuvant modality to radiation therapy, but current evidence shows that this therapeutic strategy only generated inconclusive findings in terms of clinical outcomes and additional toxicity. In the GETUG12 trial,[6] which included 413 patients with high-risk local disease, radiation therapy was combined with either ADT plus a combination regimen of docetaxel, estramustine, and prednisone, or ADT alone. No significant difference in the overall survival (OS) rate (median follow-up of 7.6 years) was observed.

Another clinical study (the RTOG 99-02 clinical trial)[7] evaluated the added benefit of the combination of paclitaxel, etoposidel, and estramustine to long-term ADT plus radiation therapy, versus ADT plus radiation therapy alone in 397 patients with high-risk localised PrC. The study was terminated early due to toxicity in the form of accrued thromboembolic toxicity, as well as haematological and gastrointestinal toxicity. In non-metastatic CRPC, chemotherapy has no place and should only be considered in experimental clinical trials in locally advanced situations, as advised by AUA and EAU guidelines.[4,5,8]

CHEMOTHERAPY IN METASTATIC PROSTATE CANCER

Metastatic Castration-Sensitive Prostate Cancer

In a small proportion of patients, most presenting with high-grade disease, PrC can progress to metastatic PrC (mPrC). While localised and regional PrC are associated with a nearly 100% rate of 5-year relative survival, OS drops to 72% at 2 years and 28% at 5 years in mPrC.[2,9,10] In newly diagnosed mPrC, the first-line treatment modality is ADT, as the disease is generally castration-sensitive. However, in high-volume metastases, additional OS benefit could be obtained with a taxane, docetaxel, combined with prednisone and used as an adjuvant therapy, as suggested by the CHAARTED trial.[11]

In the CHAARTED trial, conducted by the Eastern Cooperative Oncology Group (ECOG),[11] 790 men with treatment-naïve, castration-sensitive mPrC, of which 65% had high-volume metastases (mPrC with visceral metastases or more than four bone metastases and at least one bone metastasis beyond the pelvis and vertebral column), were assigned to either combination therapy with ADT and docetaxel (six cycles of docetaxel 75 mg/m^2 every 3 weeks) or to ADT alone. After a median follow-up of 29 months, early results indicate that the combination arm demonstrated a significant OS advantage over ADT alone (median: 57.6 versus 44.0 months; hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47-0.80). Between high-volume and low-volume patients, the HRs were comparable (0.60 versus 0.63, respectively) but no statistical significance was reached in low-volume disease patients. However, a full publication is awaited in order to fully interpret the results.

The GETUG15 trial is a randomised, open-label Phase III study attempting to address the same question as the CHAARTED trial. A total of 375 castration-sensitive mPrC patients were randomly assigned to receive ADT or ADT plus docetaxel (nine cycles of docetaxel 75 mg/m^2 every 3 weeks). The difference in median survival between both arms was not statistically significant (46.5 versus 60.9 months, respectively; HR: 0.9; 95% CI: 0.7-1.2) after a median follow-up of 82.9 months.[12,13] The updated data from GETUG15 now uses the same definition of disease extent as in CHAARTED. After a median follow-up of 82.9 months, there was no statistical difference in median OS for the high-volume disease group (35.1 versus 39.0 months; HR: 0.8; 95% CI: 0.6-1.2). This difference between the two trials might partly be explained by the differences in subsequent treatment. It is still unclear whether docetaxel should be systematically used with ADT in a subgroup of castration-sensitive mPrC patients. This should at least be discussed in the high-volume situations. Further clinical data such as the expected STAMPEDE trial, the full paper from CHAARTED, and possibly a formal meta-analysis will be needed to fully interpret the results and the role of chemo-hormonal therapy in this clinical setting.

Metastatic Castration-Resistant Prostate Cancer

In the last decade, multiple therapeutic options were developed to address mCRPC, in the form of agents targeting the androgen pathway (abiraterone[14,15] and enzalutamide),[16] radium-223,[17] vaccine (sipuleucel-T),[18] and taxane-based chemotherapy (Table 1). All of the above-cited approaches except sipuleucel-T have demonstrated improved outcomes in terms of radiographic PFS. All including sipuleucel-T demonstrated a significantly prolonged OS, highlighting the weak link between PFS and survival. However, there

is no evidence of superiority of one therapeutic modality over the others as no formal head-to-head comparison is available. Furthermore, the inclusion criteria are different across the trials. In all cases, the EAU and AUA guidelines endorse multidisciplinary team management.[4,5,8]

The choice of therapy for mCRPC is not clearly defined and depends on the metastatic disease presentation, namely metastasis extent (especially the visceral locations), symptoms, localisation and rate of progression, possibly also the speed of progression, as well as the toxicity profile of each approach relative to the side-effects-associated burden already experienced by the patient, associated comorbidities, performance status, and patient preference. Abiraterone and enzalutamide were both evaluated in chemotherapy-naïve patients[19,20] and patients failing chemotherapy with docetaxel,[14,16] and demonstrated activity in both clinical settings. Radium-223 therapy is reserved for patients with extensive symptomatic bone metastases but no known visceral metastases.[4,5,21,22]

Docetaxel in chemotherapy-naïve metastatic castration-resistant prostate cancer

In chemotherapy-naïve mCRPC, the SoC was initially mitoxantrone therapy at first, following two randomised trials that demonstrated a palliative benefit in symptomatic mCRPC without any survival improvement.[23,24] Nowadays, mitoxantrone's role is minimal, if present at all. Docetaxel (75 mg/m^2 every 3 weeks) plus daily oral prednisone (5 mg twice per day) is now considered the SoC for mCRPC requiring chemotherapy-based approaches in chemotherapy-naïve patients.[8,25,26] This was established following the pivotal findings from a randomised clinical trial, the TAX-327 trial, in 1,006 men with mCRPC. Two docetaxel regimens (75 mg/m^2 every 3 weeks or 30 mg/m^2 weekly) were compared with mitoxantrone (12 mg/m^2 every 3 weeks).[27] Both treatment arms also included prednisone therapy. The first schedule of docetaxel showed significant superiority over the second docetaxel schedule and mitoxantrone in terms of OS (19.2, 17.8, and 16.3 months, respectively) and 3-year survival rates, over a wide range of patients. PSA response was higher in the docetaxel treatment groups than in the mitoxantrone group, as was the QoL benefit.[28]

However, in this study, the 3-weekly docetaxel regimen was associated with higher occurrences of Grade 3 or 4 neutropaenia. In patients who do not tolerate a docetaxel regimen of 75 mg/m^2 every 3 weeks, docetaxel can be administered more frequently, as demonstrated by a randomised Phase III trial (NCT00255606) in 361 chemotherapy-naïve patients with mCRPC.[29] Patients were randomly assigned to a schedule of 75 mg/m^2 every 3 weeks, or 50 mg/m^2 every 2 weeks. This regimen was associated with longer time to treatment failure and lower toxicity, namely Grade 3-4 events and neutropaenic infections. However, the size of the trial precludes this schedule to be considered the SoC.

In the elderly, the use of docetaxel either as a standard regimen (performance status 0 or 1) or an adapted regimen (performance status >2) was also explored. In 175 patients (aged 75 and older) docetaxel demonstrated additional benefits with an OS of 15 months and a median PFS of 7.4 months.[30] Nevertheless, the recent recommendations from the International Society of Geriatric Oncology highlight the need to manage PrC according to each patient's individual health status, not according to age.[31]

The SoC also changed from mitoxantrone plus prednisone to docetaxel therapy after the SWOG 99-16 study, in which docetaxel plus estramustine improved the median survival by 2 months when compared with mitoxantrone plus prednisone.[32] In this Phase III trial, the former combination improved OS (17.5 months versus 15.6 months, p=0.02) with a corresponding HR for death of 0.80 (95% CI: 0.67-0.97). However, docetaxel plus estramustine was associated with substantial toxicity leading to estramustine no longer being used in combination with docetaxel. A number of clinical trials have evaluated the use of other agents as a combination therapy with docetaxel and prednisone, such as dasatinib,[33] bevacizumab,[34] or aflibercept,[35] but all these combinations failed. Based on the difference between these two available taxanes, a Phase III clinical trial (the FIRSTANA study) is currently ongoing to evaluate and compare docetaxel with two doses of cabazitaxel as a first-line treatment in patients with mCRPC. This randomised, open-label, multi-centre study (NCT01308567) aims to evaluate both compounds in terms of efficacy (OS, PFS), QoL, and safety.[36]

In second-line chemotherapy for mCRPC, the EAU does not suggest a definitive treatment strategy but highlights that cabazitaxel, abiraterone, enzalutamide, and radium-223 are effective in the

post-docetaxel setting. Docetaxel re-challenging could be suggested in the second-line setting following first-line docetaxel in well-responding patients with a relapse at least 3 months after stopping first-line docetaxel. It is unclear whether docetaxel still has a place given the availability of new compounds.[37]

Cabazitaxel as a second-line chemotherapy agent

Cabazitaxel is a novel microtubule-targeted, taxane-derived agent that has demonstrated important clinical anti-tumoural activity following docetaxel failure. As a consequence, cabazitaxel was approved as a second-line modality for CRPC requiring the use of chemotherapy in combination with prednisone in chemotherapy-experienced patients.[38] Current EAU, AUA, and American Society of Clinical Oncology guidelines recommend cabazitaxel in relapsing patients with prior docetaxel therapy and good performance status.[4,5,39] The TROPIC trial[40,41] was the study supporting this treatment strategy, and which compared mitoxantrone plus prednisone with cabazitaxel plus prednisone in 755 men with CRPC progressing on docetaxel therapy. OS was improved in the cabazitaxel group (median survival of 15.1 and 12.7 months, respectively), as well as the PFS (2.8 and 1.4 months, respectively) and the 2-year OS rate (27% and 16%, respectively).

Nevertheless, cabazitaxel is associated with non-negligible toxicity, with 82% of patients experiencing Grade 3 or higher neutropaenia and 47% of patients experiencing diarrhoea (6% Grade 3 or higher). These adverse events can be effectively managed and even prevented if the patient is surrounded by an experienced team, as demonstrated by the real-life data published by Heidenreich et al.[42] This is especially true for Grade 3-4 neutropaenia and diarrhoea.

An ongoing Phase III clinical trial (PROSELICA trial, NCT01308580) will certainly provide further efficacy, dosing, and safety data on the use of cabazitaxel plus prednisone in mCRPC patients previously treated with docetaxel.[43] This randomised, open-label, multi-centre study will evaluate cabazitaxel 20 mg/m^2 versus cabazitaxel 25 mg/m^2 not only to determine the non-inferiority of cabazitaxel 20 mg/m^2 in terms of OS, but also to evaluate the safety profile, particularly the myelotoxicity, of both cabazitaxel regimens.

Table 1: Key Phase III clinical trials in metastatic castration-resistant prostate cancer.

Study	Agents	n	Indication	Inclusion criteria	HR	Δ OS (months)
TAX-327[27]	Docetaxel/prednisone vs. mitoxantrone/prednisone	1,006	mCRPC	-	0.76	+2.9
IMPACT[18]	Sipuleucel-T vs. placebo	512	mCRPC (pre-docetaxel)	Asymptomatic	0.78	+4.1
COU-AA-302[46]	Abiraterone/prednisone vs. prednisone	1,088	mCRPC (pre-docetaxel)	Asymptomatic/no visceral metastases	0.81	+4.4
COU-AA-301[14]	Abiraterone/prednisone vs. prednisone	1,195	mCRPC (post-docetaxel)	-	0.74	+4.6
PREVAIL[49]	Enzalutamide vs. placebo	171	mCRPC (pre-docetaxel)	Asymptomatic/ visceral metastases allowed (11%)	0.76	+4 (estimated)
AFFIRM[16]	Enzalutamide vs. placebo	1,199	mCRPC (post-docetaxel)	-	0.63	+4.8
TROPIC[40]	Cabazitaxel/prednisone vs. mitoxantrone/prednisone	755	mCRPC (post-docetaxel)	-	0.70	+2.4
ALSYMPCA[21,22]	Radium-223 vs. placebo	921	mCRPC	No visceral metastases	0.70	+2.8

mCRPC: metastatic castration-resistant prostate cancer; HR: hazard ratio; OS: overall survival.

Salvage hormonal therapy with novel agents

Abiraterone

Abiraterone acetate is a CYP17A1 inhibitor that inhibits the synthesis of testosterone at the adrenal level and plays a major role at the intracrine level by suppressing androgen synthesis in intraprostatic cells. It has to be used in conjunction with prednisone 10 mg daily. It has demonstrated significant benefits in OS in key Phase III trials, in both docetaxel-naïve and docetaxel-experienced mCRPC patients.[14,20,44] In 1,195 mCRPC docetaxel-experienced patients,[14,44,45] abiraterone plus prednisone significantly improved OS over placebo plus prednisone (median: 15.8 versus 11.2 months; HR: 0.74; 95% CI: 0.64-0.86), as well as time to PSA progression and radiographic PFS. Comparable results were observed in a Phase III trial in 1,088 chemotherapy-naïve patients who were randomised to either abiraterone plus prednisone or placebo plus prednisone.[15,20,46] After a median follow-up of 49.2 months, abiraterone demonstrated significant and meaningful prolonged OS (median: 34.7 versus 30.3 months; HR: 0.81; 95% CI: 0.70-0.93).[46]

Enzalutamide

Enzalutamide is an androgen receptor antagonist that demonstrated important clinical activity in CRPC. Its affinity for the androgen receptor is higher compared with the previously available antagonists, and it has a specific mode of action with the inhibition of receptor trafficking from the cytoplasm to the nucleus. In the AFFIRM trial, 1,199 docetaxel-experienced patients were randomised to receive enzalutamide or placebo.[16,47] After a median follow-up of 14.4 months, improved median survival was observed in the enzalutamide group versus placebo (18.4 months versus 13.6 months), as well as improved PSA response, radiographic PFS, and QoL.

The Phase III PREVAIL study[19] aimed to evaluate the efficacy and safety of enzalutamide in 1,717 mCRPC patients who were chemotherapy-naïve. Median OS (risk of death, HR: 0.71; p<0.0001) was significantly higher in the enzalutamide arm compared with placebo. This trial led to an EMA indication extension for chemotherapy-naïve patients in October 2014.[48] Updated results were presented at EAU 2015[49] based on 784 deaths. The overall results were confirmed (OS: HR: 0.77; 95% CI: 0.67-0.88; p=0.0002) and a 4-month improvement in median survival with enzalutamide (35.3 months [95% CI: 32.2 - not yet reached]) versus placebo (31.3 months [95% CI: 28.8-34.2]). After a median follow-up of 31 months, 52% of enzalutamide and 81% of placebo patients received ≥1 subsequent life-extending PrC therapies.

Other chemotherapy strategies beyond first and second-line

Given the lack of Phase III trial data, there is no current SoC for patients progressing on cabazitaxel therapy, and treatment modalities following taxane failure are limited, mostly based on limited Phase II cohorts at best. Third-line salvage strategies for taxane-refractory mCRPC include platinum-based regimens such as carboplatin, either in combination with docetaxel[50] or paclitaxel.[51] In Phase II clinical studies both regimens yielded further additional benefits, although modest, with median OS of 12.4 and 9.9 months, respectively. However, the available experience has been obtained before the availability of abiraterone, enzalutamide, or radium-223.

Oxaliplatin was also evaluated in three Phase II studies in heavily pre-treated CRPC patients, in combination with 5-fluorouracil,[52] capecitabine,[53] or pemetrexed.[54] Median OS was 11.4, 5.5, and 11.9 months, respectively, with manageable toxicities. Cisplatin was also evaluated in combination with prednisone in 25 men who were refractive to docetaxel; 23% of patients with measurable disease displayed a partial response (median PFS: 6 months; OS: 55 weeks).[48]

Emerging new agents in ongoing clinical trials

Emerging non-hormonal therapies that are currently being evaluated include novel immunotherapies such as sipuleucel-T - an autologous-registered and FDA-approved prostatic acid phosphatase,[18,55] ProstVac-VF - a PSA-targeted poxviral-based vaccine,[56] and nivolumab - an anti-PD1 antibody.[57] Small molecule inhibitors such as custirsen[58-60] are also currently being investigated in order to expand the therapeutic armamentarium for the remaining unmet needs in advanced PrC. Considering the lack of survival benefit, the development of tasquinimod was stopped, according to a press release April 16, 2015.

CONCLUSION

Contrary to many other malignancies, CC is still reserved for few clinical settings within PrC. These settings have been the subject of major clinical

research in past decades, since they represent important unmet needs. While abiraterone and enzalutamide were first evaluated in patients following failure of docetaxel, recent clinical data demonstrate improved OS and good safety profiles in chemotherapy-naïve mCRPC for both new agents. Additionally, the indications for CC could be extended to selected ADT-naïve mPrC patients following the promising results of the CHAARTED trial on docetaxel combination therapy with ADT, which could very well challenge the current paradigm. However, uncertainty remains regarding the optimal target population, based on the conflicting results available. Long-term results from both these studies and ongoing trials will help further ascertain the role of chemotherapy in PrC, and will help refine the most appropriate treatment strategies for mPrC.

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HOLMIUM LASER ENUCLEATION OF THE PROSTATE (HoLEP): OUR EXPERIENCE WITH THE LEARNING CURVE AND THE DEVELOPMENT OF THE 'EN-BLOC NO-TOUCH' TECHNIQUE

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ABSTRACT

Background: Holmium laser enucleation of the prostate (HoLEP) is a safe and effective therapeutic option in patients suffering from benign prostatic hyperplasia (BPH) of any size. In spite of its excellent and durable outcomes, HoLEP is gaining widespread acceptance very slowly, since it is perceived as requiring significant endoscopic skill and having a steep learning curve. Here we present our 4-year experience with this technique after more than 200 cases, describing our learning curve with the traditional three-lobe technique of Gilling, and its progressive modification into the so-called 'en-bloc no-touch' technique.
Methods: From January 2011 to December 2014, 200 consecutive patients diagnosed with symptomatic and obstructive BPH underwent HoLEP in our department. Demographic and clinical data were prospectively collected. Age, total operating time, enucleation time and efficiency, morcellation time, energy employed, adenoma weight, hospital stay, and complications were recorded.
Results: The HoLEP learning curve in our department included an initial 1-year experience with the traditional technique of Gilling, and its progressive modification with the development of the so-called 'en-bloc no-touch' approach, subsequently standardised step by step. At the beginning of the learning curve short time intervals between the procedures are relevant for faster learning. With time and experience, adenomas of all sizes are treated, with significantly shorter total operating and enucleation times, significantly increased enucleation efficiency, decreased use of energy (meaning fewer postoperative voiding symptoms), and fewer complications. Morcellation time is more device-dependent than surgeon-dependent, and is also influenced by the composition of the adenomatous tissue.
Conclusion: The 'en-bloc no-touch' technique seems to simplify the procedure, making it easier to teach and to learn. HoLEP safety and efficacy are improved by increasing experience, as expected, but apparently also by the application of our modified and standardised procedure.

Keywords: Prostatic hyperplasia, holmium laser enucleation of the prostate (HoLEP), lasers.

INTRODUCTION

Holmium laser enucleation of the prostate (HoLEP) - introduced in 1998 by Peter Gilling et al.[1] - is an endoscopic procedure mimicking open prostatectomy and allowing complete anatomic removal of the prostatic adenoma. Over the past decade HoLEP has been proven to be a well-tolerated and effective therapeutic option[2-4] in patients suffering from benign prostatic hyperplasia (BPH) of any size.[5,6] Therefore HoLEP currently represents a valid alternative to both transurethral resection of the prostate (considered the reference standard treatment for small, <30-40 ml, and medium-sized, 40-80 ml, prostates),[2,4-6] and open prostatectomy (still taken into account

for larger prostates, >80-100 ml, by most guidelines).[7,8] HoLEP obviates the complications of open surgery and using saline as an irrigant avoids the risk of transurethral resection syndrome, increased in cases of large prostates, which are technically more difficult to resect safely and quickly. Thus, HoLEP is also cost-effective.[9]

In spite of its excellent and durable outcomes, HoLEP has proved to be slow in gaining widespread acceptance, since it is perceived as requiring significant endoscopic skill and having a steep learning curve (30-50 cases).[10,11] Furthermore, there is an additional learning curve during transition from medium-sized to both smaller and larger prostates.[12-14] Consequently, some urologists prefer more invasive and expensive options, such as laparoscopic[15,16] or robotic[16,17] simple prostatectomy. For these reasons, modular training HoLEP programmes are now available to enable safe and efficient learning of this technique.[18] Despite this, being considered technically difficult to perform, HoLEP is still limited to expert teams at high volume centres in Italy. We started performing HoLEP at our department in January 2011 and here we present our 4-year experience with this technique after more than 200 cases, describing our learning curve with the traditional three-lobe technique of Gilling[19] and its progressive modification into the so-called 'en-bloc no-touch' technique.

METHODS

From January 2011 to December 2014, 200 consecutive patients (none on anticoagulant or antiplatelet medication) diagnosed with symptomatic and obstructive BPH underwent HoLEP in our department, performed by a single surgeon (C.M.S.) with associated fellows. A continuous flow 26 Fr Storz resectoscope equipped with 12° optics and a 550-µm end-firing laser fibre were employed. The 100W Versapulse holmium laser (Lumenis) was used (2 J/50 Hz). In three cases we used the 120W Versapulse holmium laser (Lumenis) (2 J/30 Hz/medium-long pulse duration). Morcellation was performed using a 24 Fr rigid nephroscope (Storz) and the Versacut mechanical morcellator (Lumenis). Demographic and clinical data were prospectively collected. Age, total operating time, enucleation time and efficiency, morcellation time, energy employed, adenoma weight, hospital stay, and complications were recorded.

OUR INITIAL LEARNING CURVE APPLYING THE TRADITIONAL THREE-LOBE TECHNIQUE

We started performing HoLEP autonomously in January 2011, after some tutoring with experts. The data relative to our first 19 procedures, performed according to the traditional three-lobe technique, are shown in Tables 1 and 2. There was one long-term stress urinary incontinence, no transient stress urinary incontinences (only urgent micturitions), two intraoperative bleedings requiring additional haemostasis with the bipolar resectoscope (10%), and one (5%) recatheterisation the night after catheter removal (and subsequent successful removal). During this first part of the learning curve we thoroughly analysed the steps that we considered critical and difficult to perform:

1) Finding the correct plane between prostatic capsule and adenoma three times during the procedure, at 5, 7, and 12 o'clock, with the risk of enucleating in an incorrect plane within the adenoma, to perforate the capsule and/or to undermine the bladder neck at the beginning of the procedure.

2) Performing an adequate 12 o'clock incision, avoiding significant bleeding if too deep or a too-distal descent towards the sphincter.

3) Affording the rotation of the lateral lobes around the axis of their residual attachment to the bladder neck, while progressing with their enucleation, without losing the correct orientation.

4) Obtaining a clear vision of the mucosal strip from 10 to 2 o'clock, for its safe incision maximally preserving the external sphincter.

DEVELOPMENT OF THE 'EN-BLOC NO-TOUCH' TECHNIQUE

Trying to find a solution to our difficulties, time after time we introduced alterations in the traditional three-lobe technique of Gilling, progressively developing the so-called 'en-bloc no-touch' technique, which we applied in our daily routine in more than 200 BPH patients. Other authors in the past had already introduced modifications of the traditional technique in order to simplify it.[14,20]

Table 1: Data relative to patients undergoing HoLEP in 2011.

Year	Age range, years	Number of procedures	Procedures per month	Mean adenoma weight ± SD, g
2011	61-88	19	1-2	43.5±33.5

HoLEP: holmium laser enucleation of the prostate; SD: standard deviation.

Table 2: Data relative to HoLEP procedures in 2011.

Year	Total operating time ± SD, min	Enucleation time ± SD, min	Enucleation efficiency, g/min	Energy employed ± SD, kJ	Morcellation time ± SD, min
2011	88.0±35.4	60±28	0.7	156±69	14±11

SD: standard deviation; HoLEP: holmium laser enucleation of the prostate.

Why 'En-Bloc'

Adenoma enucleation begins at the apex lateral to the verumontanum, usually on the left side. The cleavage plane between adenoma and capsule is prominent at this site and particularly easy to identify. This incision between left and median lobe can be retrogradely deepened and widened towards the bladder neck, but this step is optional (partially 'en-bloc' approach, most frequently applied, obtaining a final horseshoe-like adenoma). Otherwise, the dissection is carried out without separating the median and the lateral lobes, with an intact prostatic urethra (complete 'en-bloc' approach). In both cases the correct plane has to be identified only once instead of three times, reducing the risk of error.

The left lobe is then isolated from the apex towards the bladder neck in a side-to-side manner, ascending cranially from 5 to 3 o'clock (Figure 1). Its detachment is completed from 3 to 12 o'clock and goes on towards the right side from 12 to 9 o'clock. Going back to the initial left apical incision - when performed - the mucosa is horizontally incised above the verumontanum, reaching the apex of the right lobe; the median lobe is then isolated, reaching the bladder neck, and remains attached to the right lobe. Enucleation of the right lobe goes on as described for the left lobe, from 7 to 9 o'clock, circumferentially joining its already detached superior part from 9 to 12 o'clock. The enucleated 'en-bloc' adenoma is now fixed from 10 to 2 o'clock only by a residual urothelial strip (while behind it the adenoma is almost completely detached) (Figure 2), which has to be incised before pushing the adenoma within the bladder under direct vision, limiting the risk of potential sphincteric damage. This progressive 'en-bloc' enucleation of the adenoma kept in place until the very last steps of enucleation by the anterior mucosa avoids its bothersome mobility. Two oblique incisions are finally made on the residual mucosa of the lateral lobes, and a final horizontal incision is performed on the residual mucosal strip at 12 o'clock, as proximal as possible to the bladder neck. Now the completely enucleated adenoma can be pushed inside the bladder lumen for morcellation.

Why 'No-Touch'

The mucosa at the apex lateral to the verumontanum is initially incised, but afterwards the capsular plane is mainly developed using blunt dissection. The adenoma is detached lifting it with the beak of the endoscope, serving as the surgeon's finger during open simple prostatectomy, and progressively uncovering the correct capsular plane under vision (Figure 1). The laser energy is mainly employed to release the connective shoots put in tension by pushing the adenoma away from the capsule. Vision is optimal, blood vessels can be easily identified in advance (Figure 3) and can undergo targeted haemostasis, defocusing the laser to 2-3 mm. The laser fibre is activated at a short distance from the tissue, most commonly dissolving rather than incising it. This effect is particularly evident using the 120W device, reducing laser frequency and employing the medium-long pulse length. In this way, small adenomas and areas of strongly adhering capsule may be afforded

without capsular perforation. Both the use of mechanical detachment and the 'no-touch' approach allow less energy supply to the capsular plane, implying fewer postoperative voiding symptoms.

Clinical Outcomes

From 2012 HoLEP was always performed according to the described 'en-bloc no-touch' technique, standardised step by step. The hospital stay ranged from 2 to 3.5 days for all patients, the first day being the day of surgery, the second postoperative day being the day of irrigation removal as well as catheter removal when possible a couple of hours afterwards, and the third postoperative day being the alternative day of catheter removal early in the morning. Since our hospital does not have an emergency department the current policy is to monitor spontaneous voiding for 24 hours after catheter removal, before sending the patient home.

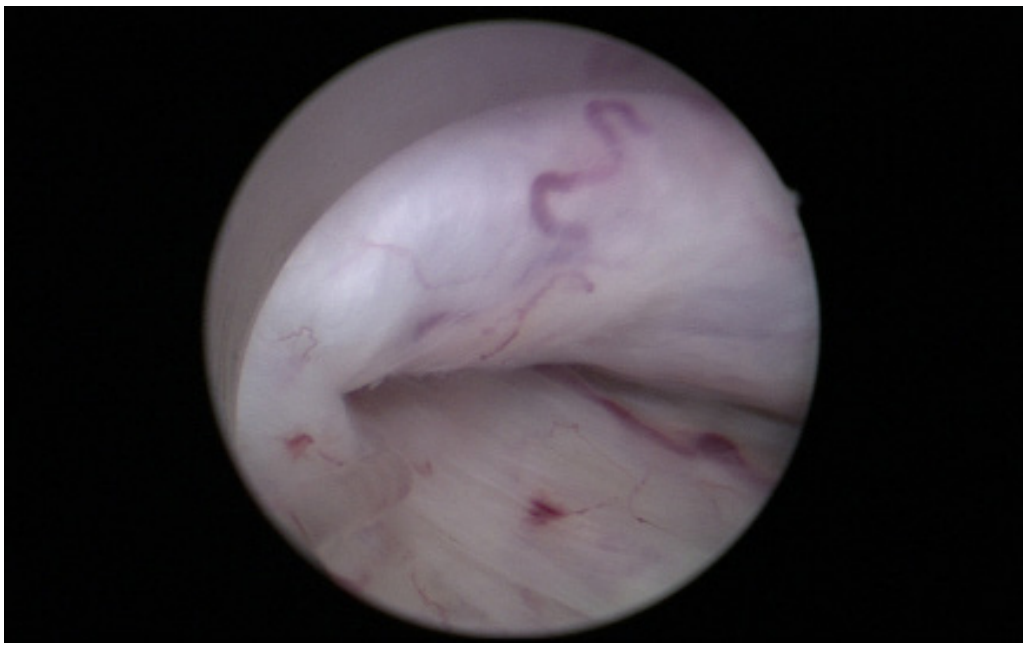

Figure 1: 'No-touch' enucleation of a prostatic adenoma, clear identification of the correct plane between left lobe and capsule.

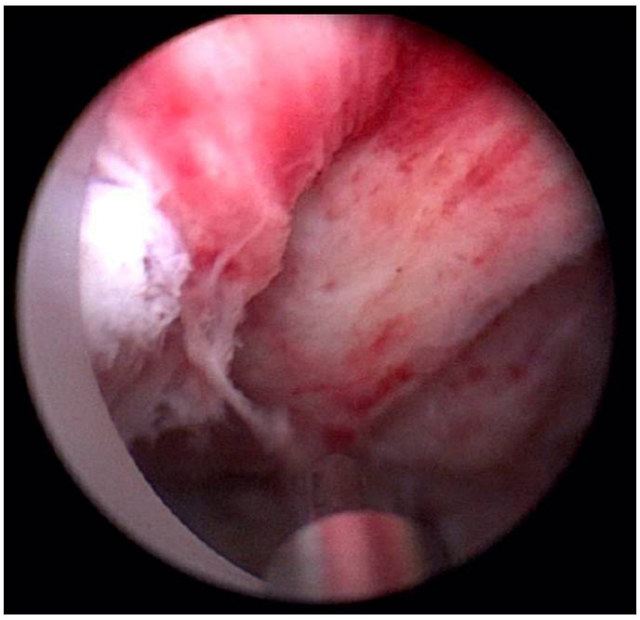

Figure 2: The final mucosal strip from 10 to 2 o'clock.

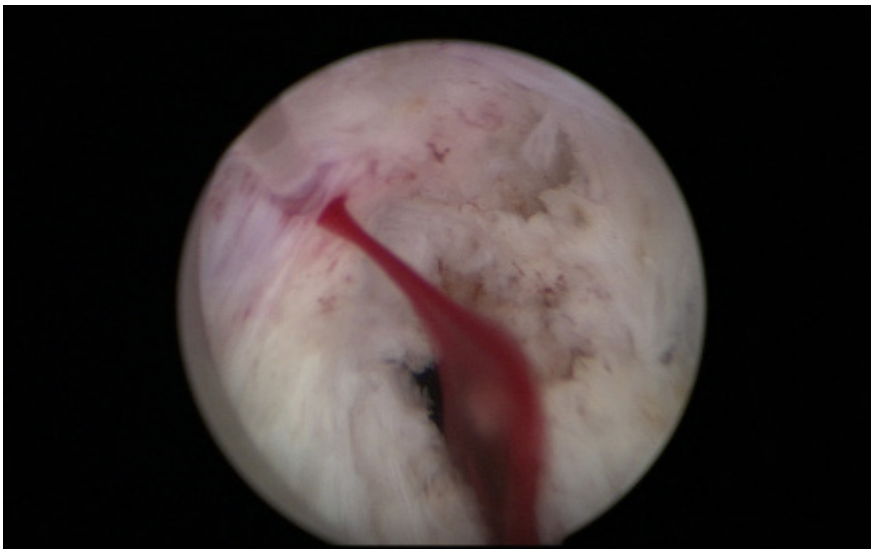

Figure 3: Targeted haemostasis of a capsular artery by defocusing the laser fibre.

Table 3: Data relative to patients undergoing 'en-bloc no-touch' HoLEP from 2012 to 2014.

Year	Age range, years	Number of procedures	Procedures per month	Mean adenoma weight ± SD, g
2012	54-83	34	3	42.1±25
2013	53-87	79	>7	52.1±41
2014	51-85	60	>7	57.7±40

SD: standard deviation; HoLEP: holmium laser enucleation of the prostate.

Table 4: Data relative to 'en-bloc no-touch' HoLEP procedures from 2012 to 2014.

Year	Total operating time ± SD, min	Enucleation time ± SD, min	Enucleation Efficiency, g/min	Energy employed ± SD, kJ	Morcellation time ± SD, min
2012	65.6±20	39.8±17	1.00	91.7±28	7.6±4.3
2013	59.9±28	30.3±13	1.72	82.0±28.8	10.9±13.5
2014	58.8±25	32.0±15	1.8	85.0±31	9.0±7.4

SD: standard deviation; HoLEP: holmium laser enucleation of the prostate.

As shown in Table 3 and Table 4, HoLEP efficiency was globally increased, performing the procedure more frequently in 2013 and 2014 than in 2011 and 2012 (from 1-3 to >7 times a month). Year after year prostatic adenomas of increasing volumes were removed with shorter total operating times, employing less time for the enucleation and less energy as well. The small increase in the morcellation time (which is more device-dependent than surgeon-dependent) is related to the corresponding increase in adenoma weight removed. In 2012 there were three patients (8.8%) requiring postoperative endoscopic haemostasis, in 2013 two (2.5%), and in 2014 one (1.7%). There were neither long-term nor transient stress urinary incontinences (only urgent micturitions during the first 10-15 days after catheter removal). Overall, seven patients (4%) required recatherisation, followed by successful catheter removal.

CONCLUSION

The HoLEP learning curve in our department included an initial 1-year experience with the

traditional technique of Gilling, and its progressive modification with the development of the so-called 'en-bloc no-touch' approach, subsequently standardised step by step. At the beginning of the learning curve, short time intervals between the procedures are relevant for faster learning. With time and experience, adenomas of all sizes can be treated, with significantly shorter total operating and enucleation times, significantly increased enucleation efficiency, decreased use of energy (meaning fewer postoperative voiding symptoms), and fewer complications. Morcellation time is more device-dependent than surgeon-dependent, and is also influenced by the composition of the adenomatous tissue.[19] The 'en-bloc no-touch' technique appears to simplify the procedure, making it easier to teach and to learn. HoLEP safety and efficacy are improved by increasing experience as expected, but apparently also by the application of our modified and standardised procedure.

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HOLMIUM LASER ENUCLEATION OF THE PROSTATE (HoLEP) IN AMBULATORY SURGERY

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ABSTRACT

The focus of this work is the need to give an update on the holmium laser enucleation of the prostate (HoLEP) technique in ambulatory surgery. Indeed, over the last two decades, there has been a significant change in surgical treatment of benign prostatic hyperplasia. Laser surgery has been growing in popularity as an alternative to standard transurethral prostatectomy. Our goal was to analyse the opportunity to perform HoLEP in one-day surgery. Furthermore, there is a willingness of the French Ministry of Health to develop this kind of management. A pilot study was performed in 50 selected patients to evaluate HoLEP feasibility in ambulatory surgery from June 2013 to April 2014. The results were good with minimal morbidity and a high satisfaction rate, but excellent organisation is necessary, leaving no room for improvisation.

Keywords: Holmium laser enucleation of the prostate (HoLEP), ambulatory surgery, benign prostatic hyperplasia (BPH).

INTRODUCTION

The surgical treatment of benign prostatic hyperplasia (BPH) has been dominated by transurethral resection of the prostate (TURP) for many decades. Indeed, TURP is the first-line 'minimal' treatment of BPH and provides excellent long-term outcomes. However, as technology has evolved the surgical management of BPH has changed in the past few years, with laser prostatectomy increasing in popularity after the development of the holmium laser enucleation of the prostate (HoLEP) technique in 1998[1] and the introduction of green light laser vaporisation in 2000.[2] Laser prostatectomy may have several advantages, including lower risk of clot retention, shorter catheterisation time, and shorter hospital stay.[3] Furthermore, some studies have shown favourable outcomes after HoLEP, even in men who underwent surgery while on anticoagulation.[4]

On the other hand, in the interest of economy, the French Ministry of Health asks us to perform 60% of ambulatory surgery in 2016. Therefore, with the French Holmium Users Group (HUG), we decided to perform a pilot study to show the feasibility of this technique in day-case surgery. Three centres participated in this study: CHU Bordeaux, Clinique Saint-Joseph Paris, and CH Aix-en-Provence.

PATIENTS

The study group comprised a cohort of 50 patients undergoing HoLEP scheduled as a day-case procedure by several experienced surgeons (having performed >50 procedures) between June 2013 to April 2014. We decided to exclude from the study patients receiving anticoagulants, with acute urinary retention (AUR), and an American Society of Anesthesiologists (ASA) score >2. Elsewhere, no limit of prostatic volume was imposed. The mean patient age was 63.2 years (range: 46-75 years), mean prostate volume was 75.3 cm^3 (range: 35-148 cm^3), mean maximum urinary flow rate was 9.3 ml/s (range: 3-20 ml/s), mean post-void residual volume was 180 ml (range: 0-452 ml), and mean international prostate symptom score (IPSS) was 23/35 (range: 8-35).

RESULTS

The conversion rate to conventional hospitalisation at the end of Day 1 was 4% (two cases of haematuria with clots). The return rate of micturition at Day 2 was 91%. After 3 months of follow-up the readmission rate was 16%. For seven patients, the cause of readmission was AUR without clots, which required bladder catheterisation and administration of alpha-blockers over 24 hours. One patient experienced a melaena and required hospitalisation for 48 hours; the cause was not found.

The complication rate was 46% Clavien Grade 1 (haematuria +/- clots, AUR, and stress incontinence), 22% Clavien Grade 2 (urinary tract infections and urgency +/- incontinence), and 2% Clavien Grade 3 (melaena). The global satisfaction rate was 99%. At 3 months follow-up, the mean prostate volume was 26 cm^3 (range: 15–62 cm^3), mean maximum urinary flow rate was 27 ml/s (range: 6.2-62 ml/s), mean post-void residual volume was 20 ml (range: 0-92 ml), and mean IPSS was 4/35 (range: 0-12).

DISCUSSION

This study confirmed the feasibility of HoLEP as a day-case surgery for selected patients. The discharge pathway is associated with minimal morbidity and short-term results are in accordance with the available literature on HoLEP.

It is nonetheless important to note that excellent organisation is necessary to be successful, which leaves no room for improvisation. This means that there should be training of care teams, informing of patients, and a written protocol. Training teams begins in consultation where the nurses must be convincing when they speak about ambulatory surgery. For the operating room, it is essential to respect schedules (early in the morning), to prepare the surgical materials, and to include the anaesthetists in this project. Finally, the nurses of the ambulatory surgery unit should be reassured. Informing patients requires a dialogue and a complete written document. Concerning the protocol, it should contain the following information: stop drinking 2 hours before surgery; first patients of the day should stop irrigation after arrival in the 1-day surgery department, and should start to drink as soon as possible; for patients discharged before 8 pm, the bladder catheter will be removed at home by a nurse the following day or the day after that (according to the team), and a follow-up phone call made 4 hours later. Ten patients benefited from spinal anaesthesia and 40 patients from general anaesthesia; we did not see a difference in results between these two groups.

There are very few studies on BPH day surgery. One study informs us of the readmission rate (3.7%) following outpatient urological surgery. The risk factors are history of cancer, bleeding disorder, male gender, ASA score 3 or 4, and age.[5] Two published articles study HoLEP as a day-case surgery in 65 and 30 patients, respectively, with near identical results.[6,7] The limitation of these studies is the small number of patients. Therefore, the results only allow for the confirmation of the feasibility of this ambulatory intervention by an experienced operator, although it is currently impossible to define predictors of failure with this coverage. Further studies are therefore required.

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EVOLVING TECHNIQUES FOR SURGICAL TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

The management of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) is one of the most topical areas in urology. Although most patients are adequately managed conservatively, many still require surgery to reduce bladder outlet obstruction or relieve symptoms by removing the inflamed adenomatous tissue. Transurethral resection of the prostate (TURP) remains the gold standard treatment in all national and international guidelines, with open prostatectomy and laser enucleation reserved for patients with a prostate >80 ml. The current trend in the surgical management of BPH is threefold: replacing open prostatectomy with transurethral enucleation of the adenoma, managing high-risk patients by photoselective vaporisation of the prostate thus minimising blood loss, and moving BPH surgery to ambulatory day surgery and one-day surgery units in selected patients. Laser enucleation has been pioneered using the Holmium laser, although the GreenLight™ laser has been recently proposed as an alternative approach. The absence of any bleeding in photovaporisation of the prostate allows surgery to be performed in a growing population of patients on anti-aggregant and anticoagulant medications. Randomised trials of the GreenLight XPS™ laser with the MoXy™ fibre versus TURP proved the effectiveness of photovaporisation in the surgical management of BPH and suggested that 50% of patients could be discharged within 24 hours. The demand for BPH surgery remains high and urologists have rapidly adapted to the increasing demand for minimally invasive surgery. Prostate surgery evolved from a heroic procedure that remained in the memories of the entire patient family for life into a day-case procedure, and the future hopefully holds ejaculation-sparing surgery.

Keywords: Prostatic hyperplasia, transurethral resection of the prostate (TURP), holmium laser enucleation of the prostate (HoLEP), GreenLight, laser.

INTRODUCTION

Several guidelines for the management of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) are available. Transurethral resection of the prostate (TURP) is still considered the standard surgical treatment of BPH for prostates up to 80 ml, with open adenomectomy and holmium laser enucleation of the prostate (HoLEP) reserved for larger prostates.[1,2] For many years the major challenge of prostate surgery was to reduce complications, particularly intra and post-operative bleeding, with the consequent need for blood transfusion. This shortens hospital stays, which reduces costs and accelerates patient recovery, therefore decreasing the societal cost of the disease. Most of these goals were achieved with transurethral surgery, although the management of large prostates remained a challenge. The development of bipolar TURP helped in reducing the complications associated with longer operative time and allowed for the safer management of patients with cardiac pacemakers, meaning larger prostate volumes could be resected. Two major issues that remained unresolved with TURP were the management of high-risk patients on anticoagulants or antiplatelet drugs, and the management of BPH surgery as a

day case. The development of HoLEP provided a viable alternative to open adenomectomy, making the open approach obsolete.[3] Notwithstanding a long learning curve and the problems associated with morcellation, the HoLEP technique has gradually gained popularity, although it is usually performed by a single surgeon in most centres.

Vaporisation of the prostate with the GreenLight™ laser is one of the few alternatives to TURP that found its way into most guidelines on the management of BPH.[1,2] Photovaporisation of the prostate with the GreenLight laser was introduced in the early 2000s, with the first paper published in 2003.[4] The laser was limited in power (80 W), but the concept of prostate vaporisation with negligible blood loss, rapid removal of the indwelling catheter, and early patient discharge was proven. The particular wavelength of the GreenLight laser (532 nm) allowed the energy to be electively absorbed by oxyhaemoglobin with a previously unknown level of haemostasis that made bladder irrigation obsolete. Improvement of the laser technology allowed the development of more powerful systems that were able to deliver 120 W (GreenLight HPS™) and finally 180 W (GreenLight XPS™).[5,6] With the latter version of the laser came a new version of the glass fibre (MoXy™ fibre) and up to 650 kJ could be delivered. This new fibre includes a larger emission window and incorporates an irrigation channel that helps to extend the fibre function.[7]

Randomised studies of the GreenLight XPS laser versus TURP have definitively proven the effectiveness of photovaporisation.[8,9] According to the GOLIATH study[8,9] (a randomised non-inferiority study of TURP versus GreenLight XPS), TURP and GreenLight XPS offer comparable improvement of the signs and symptoms of BPH at 6 and 12 months. TURP remains a shorter procedure compared to photovaporisation with an average operative time of 39.3 minutes versus 49.6 minutes, but the 10 extra minutes required for the GreenLight XPS procedure result in a significant difference in the post-operative parameters compared with TURP: a shorter time in the recovery room (2.2 hours versus 2.9 hours); a shorter catheterisation time (40.8 hours versus 59.5 hours); a shorter time to health status (patients able to void with a post-void residual urine volume <100 ml [37.3 hours versus 63.5 hours]); and shorter hospital stay (65.5 hours versus 96.9 hours). Photovaporisation of the prostate has been associated with significant post-operative symptoms but the GOLIATH study proved that this was a false perception as the incidence of irritative symptoms/pain and discomfort was 19.1% in the GreenLight group and 21.8% in the TURP group. Evaluation of prostate volume showed a comparable reduction of prostate volume in the two arms, with a decrease from 48.6 ml to 23 ml in the GreenLight group and from 46.2 ml to 20.4 ml in the TURP group.

The comparison of photovaporisation of the prostate and open adenomectomy is something of a historical question as the number of open surgical procedures for BPH are rapidly decreasing worldwide, and enrolling patients in randomised studies of endoscopic versus open procedures is increasingly difficult. In 2007 Alivizatos and co-workers[10] published the results of a randomised study of the old GreenLight 80 W versus open adenomectomy in patients with prostate volume >80 ml. The photovaporisation procedure was longer than open surgery (80 minutes versus 50 minutes), but catheter time was shorter (24 hours versus 120 hours), as well as hospital stay (48 hours versus 144 hours). At 12 months similar results were observed for the International Prostate Symptom Score (IPSS) (9 versus 8), maximum flow rate (16.0 ml/s versus 15.1 ml/s), post void residual (17 ml versus 12 ml), sexual function (International Index of Erectile Function [IIEF] score 12 versus 12), and post-operative prostate-specific antigen (2.4 ng/ml versus 2.0 ng/ml). Open surgery resulted in a better quality of life (QoL): IPSS question 8 (1 versus 1) (p=0.035 because of a better standard deviation for open surgery) and lower prostate volume (55 ml versus 10 ml). At 12 months adverse events were observed in 21.5% of GreenLight patients and in 31.7% of the open surgery patients. A more recent analysis of GreenLight and open surgery patients suggests a significant economic advantage for the laser treatment with an additional cost of €1450 for open surgery due to a longer hospital stay (3.0 days versus 10.4 days), and a higher reoperation rate in the open surgery group (19.5% versus 1.9%).[11] The study was limited by the retrospective analysis of the open surgery data and by the unfavourable outcome of the open surgery patients compared with other published series.[11]

Long-term data of GreenLight vaporisation first became available in 2008 when Ruszat et al.[12] published their 5-year data showing the durability of the results in terms of lower urinary tract symptoms, QoL, and flow rate parameters. Analysis

of the long-term outcome of two case series of GreenLight 80 W and TURP showed comparable functional outcomes at 5 years, although the reoperation rate was higher in the laser group compared to the TURP group (18% versus 3% reoperation for recurrent adenoma), suggesting that the old and low-power laser unit offered an inferior tissue ablation capacity, opening the way to more powerful equipment such as the GreenLight HPS and XPS lasers that were eventually made available.[13]

After 25 years of managing patients with lower urinary tract symptoms due to BPH we believe that there is no single surgical technique that fits all patients. TURP (monopolar and bipolar), vaporisation, and enucleation techniques are here to stay, as we require all of these techniques in our departments. TURP can be the only available procedure in low-volume centres but tertiary referral institutes certainly need to have all techniques available for managing the various patients that may be referred. Although we would all like a surgical technique to have a short learning curve, an interesting study from Japan suggests that 81 procedures are required to reach a plateau in performing TURP.[14] Misrai et al.[15] recently published a figure of 50 patients as the number required to plateau the number of intra and post-operative complications with the GreenLight laser. Similar numbers (50 patients) were proposed by Shah and co-workers[16] for the learning curve of HoLEP.

The GreenLight laser is now part of the urologist's armamentarium in several centres worldwide, and the application of this new technology includes the management of patients at high surgical risk, in which maximal control of intra and post-operative bleeding and management of BPH surgery as a day case are required. Notwithstanding the obvious value of the GreenLight in managing patients on anticoagulant or antiplatelet drugs, the possibility of performing BPH surgery as a day case is the real 'game changer', the potential of which has not been fully explored or implemented. Although the evidence in the literature is limited, the possibility of managing BPH surgery as a day case using the GreenLight laser is there, and further evidence will become available in the near future.[17]

Moving BPH surgery from a standard ward into a day-case unit in selected patients is a paramount change in terms of hospital management, and has a profound effect on the cost of BPH surgery. Patients operated on with the GreenLight laser as a day case can also be managed in different ways according to the national, regional, and local health service organisation. In most centres patients can be discharged within the same day of surgery with an indwelling Foley catheter that can be removed over the next 24 hours, alternatively patients can be discharged within 24 hours from admission without an indwelling catheter. The combination of follow-up consultations and phone calls to manage patients in the early post-operative weeks varies accordingly in different centres. Will every BPH patient scheduled for surgery be a candidate for prostate vaporisation with the GreenLight as a day case? Certainly not, but nevertheless, beyond being able to operate on patients receiving anticoagulants and antiplatelet drugs, BPH surgery as a day case is the most impressive and interesting change we have seen in this area so far.

Day-case surgery for BPH is here to stay and it will soon be widely adopted; however, research never ceases and the next issue will be ejaculation-sparing surgery. We are beginning to understand how BPH surgery impacts ejaculation, and modifications of the standard techniques have already been proposed.[18] In the third millennium the evaluation of the effectiveness of a surgical procedure should always consider not only the improvement of the clinical condition but also the foreseeable consequences and the adverse events that often come with surgery. Retrograde ejaculation remains the number one reason for BPH patients to postpone or refuse surgery.

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