EMJ EUROPEAN MEDICAL JOURNAL

UROLOGY

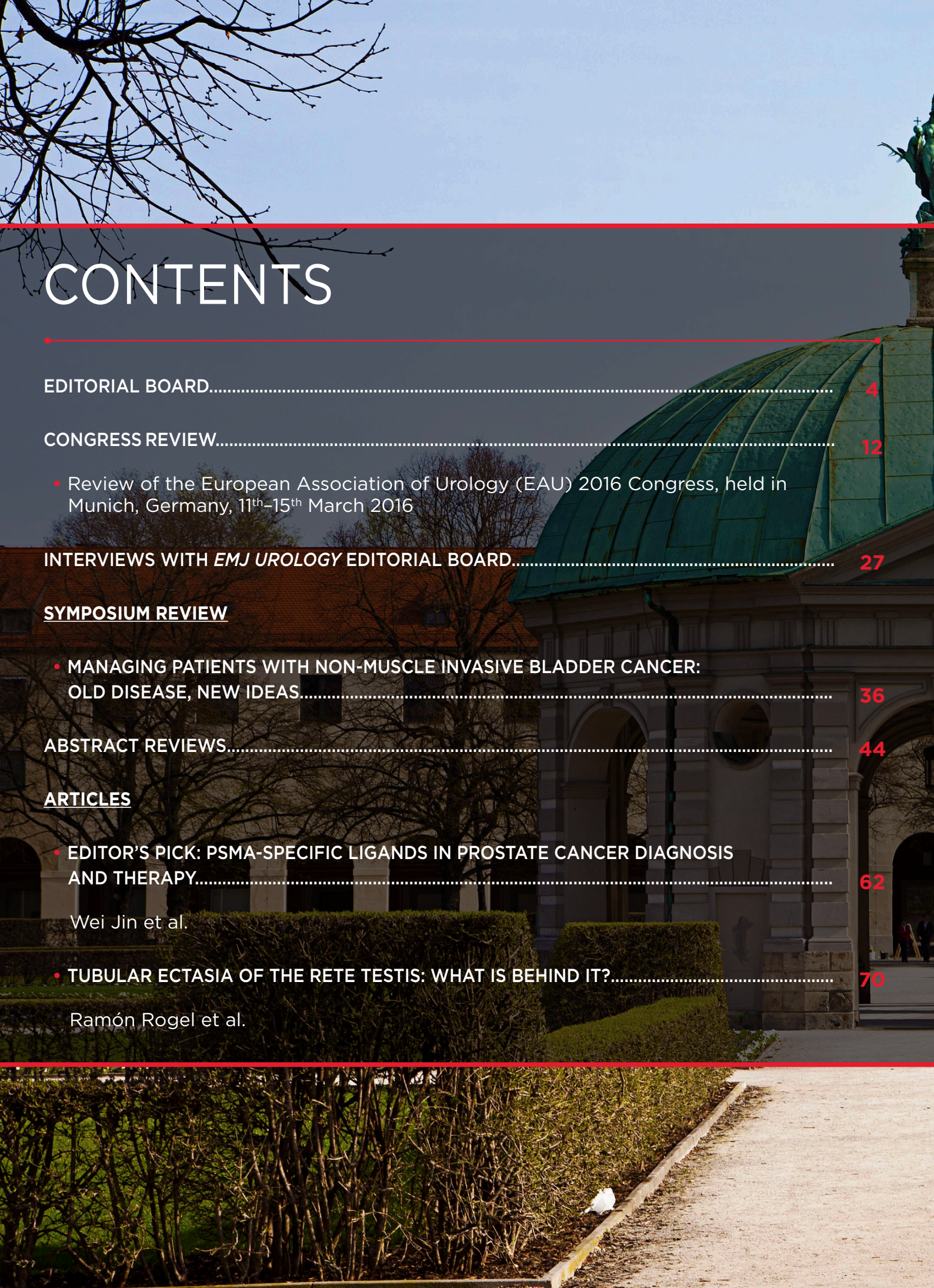
ISSN 2053-4213 Vol 4.1 • April 2016 • emjreviews.com

INSIDE

Review of

EAU 2016

Munich, Germany



CONTENTS

UROLOGY

Editorial Board

Urology

UROLOGY 4.1 | APRIL 2016

Published by the European Medical Group

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

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Welcome

Welcome to the *European Medical Journal Urology*, which will be your guide to the latest in urological practice and the recent European Association of Urology (EAU) Congress 2016. We are pleased to present a comprehensive summary of the congress, interviews with our Editorial Board, and a selection of peer-reviewed articles.

EAU16 took us to the beautiful city of Munich, Germany, this March for 5 days of presentations, discussions, and debate in the field. The outstanding quality of the work seen at the congress is a testament to the progress that has been made in urological specialties this year. Whether or not you were present, here you will find a review of the biggest news from the congress with exciting technological developments, new laboratory techniques, and research focussed on improving patients' quality of life.

In the congress review, our Editorial Board provide answers to some of the pressing questions in urology and tell us more about their own experience, where it started, and where it is going. These are an inspiring read for urologists, whether you are new to the discipline or an experienced hand!

Also in this edition, you will find abstract reviews of the congress' most influential presentations, detailing the research undertaken in a number of concise summaries. Here we see work across the spectrum of urology including: a historical perspective from Angulo, a look at new laser technology in prostate cancer from Kallidonis et al., a consideration of a new model for prostate cancer recurrence following prostatectomy by Røder et al., and many more.

The peer-reviewed articles in this edition take on the most contemporary and controversial topics in urological practice and unpick the evidence. Our Editor's Pick, from Jin et al., provides a fascinating look into PSMA-specific ligands in prostate cancer. Satyanarayan et al. bring us a review of the surgical management of post-prostatectomy incontinence. Asking the question 'tubular ectasia of the rete testis: what is behind it?', Rogel and colleagues tackle the issue in their detailed review. On top of this, we have further articles on the topics of surgical techniques, oncology, and the pathogenesis of urinary tract infections.

We hope this edition provides you with all the information you need to continue to develop and improve your own practice, as well as a suitable insight into the EAU congress. We look forward to all the developments we will be seeing in urology as 2016 continues; we will be back again at EAU17 in London, UK in March, where we hope to see you too!

Spencer Gore

Director, European Medical Journal

European Medical Journal Urology is published annually.
For subscription details please visit www.emjreviews.com

Front cover and contents photograph: Munich, Germany, home of EAU 2016.

Instillation therapies for bladder cancer have a long tradition for our company

BC CARE
by medac

BCG-medac

Mitomycin 1 mg/ml

The complete adjuvant first-line arsenal for your NMIBC patients

Exclusively by medac

Mitomycin powder for solution for infusion / Mitomycin 1 mg/ml, powder (and solvent) for solution for intravesical use.

Qualitative and quantitative composition: Powder for infusion: 1 injection vial with 50 (250) (500) (1000) mg powder contains 2 (10) (20) (40) mg mitomycin. Powder and solvent for solution for intravesical use: 1 injection vial with 500 (1000) mg powder contains 20 (40) mg mitomycin. Excipients: Powder: Sodium chloride; Solvent: Sodium chloride, water for injection. Therapeutic indications: Adenocarcinomas emanating from the bronchi, breast, stomach or pancreas. Squamous cell carcinoma emanating from the bronchi, head, neck, mouth cavity or cervix-vulva. Urothelial cancer emanating from the bladder. Mitomycin should be given intravenously in fixed combination schedules as palliative treatment for the above listed tumour forms, and in addition as part of adjuvant chemotherapy in breast cancer and cancer of the stomach. Intravesical monotherapy in superficial bladder cancer. In DK Mitomycin is only indicated in non-invasive bladder cancer and breast cancer. Posology and method of administration: Intravenous administration: 6-10 mg/m² body surface, given as a single dose, repeated every 3 to 8 weeks, depending on the treatment regime, response and side-effects. As a general rule 6 mg/m² of Mitomycin is administered every 3 weeks and 10 mg/m² is used with 4-8 week intervals. An alternative dosage is 20 mg/m² as a single dose every 6 to 8 weeks. Intravesical administration: 20-40 mg once weekly for 8 weeks. Dose reduction may become necessary if local reactions appear. In patients with low risk of tumour recurrence one immediate postoperative instillation can be used as the adjuvant treatment; most frequent dose is 40 mg. The patient should be catheterized, the bladder emptied and the solution is instilled. The solution should be kept in the bladder for 1-2 hours. Contraindications: Hypersensitivity to mitomycin or any excipient; reduced bone marrow function; breast feeding. Systemic use: Acute infections; haemorrhagic diathesis; severe liver, lung or renal disorders; poor general condition; lactation. Intravesical use: Bladder perforation, cystitis, severe reduced kidney function. Undesirable effects: Systemic administration: Very common: Cumulative bone marrow suppression, leukocytopenia, thrombocytopenia; nausea, vomiting. Common: Interstitial pneumonia, dyspnoea, cough (steroids are suitable for prophylaxis and for the treatment of existing pulmonary reactions); mucositis, stomatitis, diarrhoea, anorexia; local exanthemata, allergic skin rash, contact dermatitis, palmar-plantar erythema, alopecia; renal impairment, serum creatinine elevation, glomerulopathy. In extravasation cellulitis, tissue necrosis; local administration of dimethyl sulfoxide (99% DMSO) and the application of a dry cold compress are the recommended treatment measures. Uncommon: Fever. Rare: Life-threatening infection, sepsis, haemolytic anaemia; cardiac failure, especially after previous treatment with anthracyclines; pulmonary hypertension, pulmonary veno-occlusive disease; liver function impairment, elevated transaminases, jaundice, hepatic veno-occlusive disease; generalised exanthemata; haemolytic uraemic syndrome, microangiopathic haemolytic anaemia (MAHA syndrome). Very rare: Severe allergic reaction. Intravesical administration: Common: Local exanthemata, allergic skin rash, contact dermatitis, palmar-plantar erythema; cystitis, dysuria, nocturia, polyuria, haematuria, local bladder wall irritation. Rare: Generalised exanthemata. Very rare: Necrotising cystitis, allergic (eosinophilic) cystitis, ureteral stenosis, reduced bladder capacity. Patients should be advised to wash hands and genital area after urination following administration to avoid contact dermatitis. Legal classification: POM (prescription only medicine).

Marketing authorisation holder: medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany.

Date of revision of text: 06/2015 Mitomycin has been authorised in Denmark (20 mg only), Germany and Sweden.

BCG-medac, powder and solvent for suspension for intravesical use.

After reconstitution, one vial contains BCG (Bacillus Calmette-Guérin) bacteria seed RIVM derived from seed 1173-P2, 2 x 108 to 3 x 109 viable units. Excipients: Powder: polygeline, glucose anhydrous and polysorbate 80. Solvent: sodium chloride and water for injections. Indications: Treatment of non-invasive urothelial bladder carcinoma: 1) curative treatment of carcinoma in situ; 2) prophylactic treatment of recurrence of : a) urothelial carcinoma limited to mucosa : Ta G1-G2 if multifocal and/or recurrent tumour, Ta G3, b) urothelial carcinoma in lamina propia but not the muscular of the bladder (T1), c) carcinoma in situ. Contraindications: Hypersensitivity to BCG or to any of the excipients. BCG-medac should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (e.g., positive HIV serology, leukaemia, lymphoma), cancer therapy (e.g., cytostatic medicinal products, radiation) or immunosuppressive therapy (e.g. corticosteroids). BCG-medac should not be administered to persons with active tuberculosis. The risk of active tuberculosis must be ruled out by appropriate anamnesis and if indicated by diagnostic tests according to local guidelines. Past history of radiotherapy of the bladder. Women during lactation. BCG-medac must not be instilled before 2 to 3 weeks after TUR, bladder biopsy or traumatic catheterisation. Perforation of the bladder. Acute urinary tract infection. Undesirable effects: All patients receiving the product should be carefully monitored and advised to report all incidences of fever and other events outside the urinary tract. Systemic adverse reactions/infections are defined as: Fever > 39.5°C during at least 12 hours, fever > 38.5°C during at least 48 hours, miliary pneumonia due to BCG, granulomatous hepatitis, liver function test abnormalities, organic dysfunction (other than genito-urinary tract) with granulomatous inflammation at biopsy, Reiter's syndrome. Severe systemic BCG reaction/infection can lead to BCG sepsis which is a life-threatening situation. Infections, infestations: Very commonly cystitis and inflammatory reactions (granulomata) of the bladder. Uncommonly urinary tract infection, orchitis, severe systemic BCG reaction/infection, BCG sepsis, miliary pneumonitis, skin abscess, Reiter's syndrome (conjunctivitis, asymmetrical oligoarthritis and cystitis). Rarely vascular infection (e. g. infected aneurysm), renal abscess. Very rarely BCG infection of implants and surrounding tissue (e.g. aortic graft infection, cardiac defibrillator, hip or knee arthroplasty), cervical lymphadenitis, regional lymph node infection, osteomyelitis, bone marrow infection, psoas abscess, infection of the glans penis, orchitis or epididymitis resistant to anti-tuberculous therapy. Blood and lymphatic system: Uncommonly cytopenia, anemia. Frequency not known: Haemophagocytic syndrome. Immune system: Very commonly transient systemic BCG reaction (fever < 38.5°C, flu-like symptoms including malaise, fever, chills, general discomfort). Very rarely hypersensitivity reaction (e.g. oedema of eyelids, cough). Eye: Very rarely chorioretinitis, conjunctivitis, uveitis. Vascular: Very rarely vascular fistula. Respiratory, thoracic, mediastinal: Uncommonly pulmonary granuloma. Gastrointestinal: Very commonly nausea. Very rarely vomiting, intestinal fistula, peritonitis. Hepatobiliary: Uncommonly hepatitis. Skin, subcutaneous tissue: Uncommonly skin rash. Musculoskeletal and connective tissue: Uncommonly arthritis, arthralgia. Renal, urinary: Very commonly frequent urination with discomfort and pain. Uncommonly macroscopic haematuria, bladder retention, urinary tract obstruction, contracted bladder. Frequency not known: Renal failure, pyelonephritis, nephritis (including tubulointerstitial nephritis, interstitial nephritis and glomerulonephritis).Reproductive system, breast: Very commonly asymptomatic granulomatous prostatitis. Uncommonly epididymitis, symptomatic granulomatous prostatitis. Frequency not known: Genital disorders (e.g. vaginal pain, dyspareunia), oligospermia, azoospermia. General; administration site: Commonly fever > 38.5°C. Uncommonly hypotension. Legal classification: POM (prescription only medicine). **Marketing authorisation holder: medac GmbH, Theaterstraße 6, 22880 Wedel, Germany. Date of revision of text:** 08/2015

BCG-medac has been authorised in Austria, Belgium, Croatia (Medis Adria), Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Kazakhstan, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Sweden, Spain, Thailand and Ukraine.

NMIBC on your smartphone
Run the guidelines
Toolbox

medac

Foreword

Dr A. Erdem Canda

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

Dear Colleagues and Friends,

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

In this issue we once again have a wide variety of fascinating peer-reviewed papers, such as; 'Outcomes of salvage lymph node dissection for prostate cancer with clinical nodal relapse: results of a multicentric, retrospective study' by Marco Oderda et al., 'Renal metastasis of a malignant myopericytoma: a case report and review of literature' by Jeroen Van Besien et al., 'PSMA-specific ligands in prostate cancer diagnosis and therapy' by Wei Jin et al., and 'Pathogenesis and laboratory diagnosis of childhood urinary tract infection' by Jharna Mandal. It is hoped that you will find the content and variety of these articles both useful and stimulating to your work.

The European Association of Urology (EAU) Congress is an annual event that attracts great attention worldwide. Many sessions, debates, and courses are included in the congress across every urology subspecialty, presenting the latest developments for rigorous discussion. Within this issue of *EMJ Urology* you will find information about this year's EAU Congress, which was held on 11th–15th March 2016 in Munich, Germany. As one of the biggest urology meetings in the world, the highlights covered within this journal issue ought to be of value to everyone who has an interest in the field.

> "The European Association of Urology (EAU) Congress is an annual event that attracts great attention worldwide."

Scientific endeavour forms the heart of this journal, and this is best encapsulated by the offerings of all those who have contributed to this journal; therefore I would also like to take this opportunity to invite you all to submit your work to be published in the next edition of *EMJ Urology*, in 2017.

I hope you enjoy reading this issue!

Kind regards,

A. Erdem Canda

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

Exclusive Interviews on Prostate Cancer

(Click on video clip to view)

Reducing Prostate Cancer Progression and Mortality: What Patients Can Do to Reduce Risk

Stacey Kenfield

Developing a Self-Management Programme to Support Prostate and Testicular Cancer Survivors

Andrew Tuner

The Use of Supplements to Complement a Healthy & Balanced Diet For Prostate Cancer Patients

Robert Thomas

ASPIRE-PCa: Prospective, Global Observational Study of Men with Late-Stage Prostate Cancer

Maria De Santis

Drug Development for Metastatic Castration-Resistant Prostate Cancer

Hilary Glen

To view more of the latest videos, please click here

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13


Messe München
EAU16 | MUNICH
11-15 March 2016
Sharing knowledge - Raising the level of urological care

EAU ANNUAL CONGRESS 2016

INTERNATIONALES CONGRESS CENTER MÜNCHEN,
MUNICH, GERMANY
11TH-15TH MARCH 2016

Welcome to the *European Medical Journal* review of the 31st Annual Meeting of the European Association of Urology Congress

Being home to more than 200 biotechnology companies, and having once been voted the world's most liveable city, Munich, Germany, was a perfect host for the extensive collaboration and innovation that took place at the EAU16 congress. During this time, the city warmly welcomed the more than 13,000 attendees to the prestigious event proving their motto, 'Munich likes you', true.

Representing 118 countries and around 200 companies, delegates discussed a huge variety of ideas between the rooms and halls of the Internationales Congress Center München, Munich; these ideas were presented over the course of more than 300 sessions by 1,425 speakers. The result was that a culmination of over 4,400 scientific pieces were displayed and disseminated at EAU16. The impact of the event was clear, with almost 17,000 tweets shared by 1,600 people discussing the various innovations and information on show. "Nothing would happen without being made to happen" stated Prof Chris Chapple, EAU Secretary General, during the opening ceremony, as he spoke on the continuing efforts of urologists to bring forth new developments and challenge new issues in medicine.

An abundance of awards were presented at this year's EAU congress, where many urologists were recognised for their contributions to the field. The first award of the congress was the EAU Willy Gregoir Medal, EAU's highest honour, which was awarded to Prof Walter Artibani (Italy) for 'a significant contribution to the development of the urological specialty in Europe'. Prof Arbitani commented on how overwhelming it was to receive such an honour. The EAU Innovators in Urology award was presented to Prof Josep Maria Gil-Vernet Vila (Spain) for his work in educational surgical videos.

Prof Alberto Briganti (Italy) was one of the youngest ever recipients of the Crystal Matula award, a prize given to a promising new urological academician. The Hans Marberger award for the best paper published in the field of minimally invasive surgery in urology was given to Prof Mohan Gundeti (USA), for his fascinating paper on the use of robots for minimally invasive surgery. Finally, honorary memberships were awarded to Prof Per-Anders Abrahamsson (Sweden), Prof Jalil Hosseini (Iran), Prof Günter Janetschek (Austria),

Prof Michael Marberger (Austria), Mr Keith Parsons (UK), Dr Ying-Hao Sun (China), and Dr Vladimir Tkachuk (Russia).

A multitude of information was available at the event for all delegates to take in with a number of presentations on display that outlined significant advancements in the field. These included a study which found a number of novel non-coding RNA sequences that could be used for the detection of prostate cancer, a discovery that has the potential to reveal much more about the pathogenesis of many cancers. There was also much discussion about the improvement of patient care in a variety of contexts, such as the use of active surveillance in men with low-risk prostate cancer, and a fascinating observation of the use of telemedicine, whereby informational videos are utilised to prepare patients for surgery rather than the traditional doctor-patient interview.

> “Nothing would happen without being made to happen.”

In our review, you will find a number of short articles on the highlights from EAU so that you can catch-up on or look back at some of the innovations and ideas that arose at the congress. We also feature a number of abstracts summaries from the congress, which display the quality of the ongoing work in the field of urology. The congress was a great success, and we are already looking forward to EAU17, which will be held in London, UK in March 2017.

Novel Non-coding RNAs Provide Hope for Better Diagnostics in Prostate Cancer

GENETIC MARKERS of disease are becoming increasingly useful clinically; a recent study has found a number of novel non-coding RNA sequences that could be used for the detection of prostate cancer (PCa). The current markers, prostate-specific antigen and *PCA3*, are inaccurate, possibly leading to false positives, or failing to detect cancer. It has been suggested that a more consistent, specific test is required, one that would make population testing viable.

A growing body of research now suggests that RNA, or more specifically, sequences of RNA termed non-coding RNA, has a greater array of functions than previously thought. Importantly, non-coding RNA may be implicated in pathological processes such as cancer development.

In one study presented at EAU16, 64 PCa biopsies were reviewed, with 200 million sequences read from each sample. The result was the identification of >2,000 genes, which were significantly different in tumour samples compared with control samples, several of which showed increased sensitivity and specificity over current diagnostic markers.

> “We have several good candidate biomarkers, however we are aiming to design a test which utilises a combination of biomarkers. This will give significantly better specificity than existing tests. Our work on RNAs is allowing us to design a completely new kind of PCa test.”

Furthermore, many of these biomarkers could be reliably detected in urine.

“This is a new approach to developing diagnostic tests, and comes from applying real basic science to a practical clinical problem. Given that our initial results show a high specificity for PCa in urine tests, the prospects are good that we will be able to translate this into a better test for PCa,” explained Prof Manfred Wirth, University of Dresden, Dresden, Germany in a press release dated 13th March 2016. “We have several good candidate biomarkers, however we are aiming to design a test which utilises a combination of biomarkers. This will give significantly better specificity than existing tests. Our work on RNAs is allowing us to design a completely new kind of PCa test.”

This research is still in its infancy and has the potential to reveal much more about the pathogenesis of many cancers; for example, the team discovered one non-coding RNA, labelled TAPIR (tumour-associated proliferation-inducing RNA), that may be involved in halting the growth of cancers.

Tablets Over Talking: Is Telemedicine the Future?

'TELEMEDICINE' is becoming increasingly important in patient interactions, particularly in informing and reassuring patients. As a result, the process by which informed consent is achieved became a key talking point at EAU16 where Australian researchers compared the use of informational videos to prepare patients for surgery against traditional patient-doctor interviews.

While it is hugely important that patients understand the medical procedures that they are to undergo, frequently patients give consent without full comprehension of the procedure. In a recent randomised controlled study, 80 patients undergoing surgery for acute renal colic were randomised to either view a video presentation featuring a cartoon animation narrated by a doctor on an iPad or tablet (n=36), or receive face-to-face counselling with their doctor (n=44). Subsequently, lead researcher Dr Matthew Winter, Royal North Shore Hospital, Sydney, Australia, and colleagues checked for both patient understanding and satisfaction by administering questions on the procedure. Following this, patient crossover occurred; each patient then received the same questionnaire and was asked to rate their overall preference for information delivery.

"Patients often find it difficult to comprehend their planned procedure. We have found patients' knowledge is greatly improved through the use of portable video media and is their overall preferred method of information delivery compared with standard verbal communication" stated Dr Winter.

The results were significant, with 80.7% of patients conveying a preference for the video, compared with 19.3% of patients who preferred the face-to-face meeting. The study also demonstrated an improvement in patient understanding of 15.2%, thought to be related to the patients being able to appraise the video at their own pace, before reviewing the procedure with their doctor.

Commenting on the applications of the technology, Dr Winter said in a press release dated 14th March: "Informed consent for patients undergoing procedures is both an ethical and legal responsibility, and crucially important for optimising treatment.... Through the use of portable video media, a doctor can present his/her own practice and procedural technique in an innovative, dynamic, and engaging manner."

The Variable Nature of Kidney Donations Across Europe

SIGNIFICANT variations in the number of kidney transplant (KT) donors between European countries, likely as a result of

the differing legal and social standards across the continent, have been revealed in a recent study.

Kidney failure can result from a variety of disorders or events, including diabetes, injury, high blood pressure, and drug overdose. Rates of chronic kidney disease are variable across European populations, but are increasing universally. Kidney dialysis is a common treatment, but kidney donation is the most effective long-term solution. Nonetheless, the nature of kidney donation and management of their supply varies significantly from country to country.

> If countries want to increase transplant rates, and so increase survival from kidney failure, they might consider changing the way they source donor organs.

"As the technology becomes more mainstream, and rates of kidney failure are increasing, the demand for organs has increased quite significantly, and there is a general need to obtain more organs. At the moment, whether you can find a donor organ largely depends on where you live. If countries want to increase transplant rates, and so increase survival from kidney failure, they might consider changing the way they source donor organs," said Dr Víctor Díez Nicolás, Department of Urology, Hospital Universitario Ramón Y Cajal, Madrid, Spain, in a press release dated 13th March from EAU16.

The study, analysing KT activity across Europe in 2014, has illustrated the heterogeneity of kidney transplant activity across the continent. For example, there were 35.7 deceased donors per million population (pmp) in Spain, compared with 10.4 in Germany. The authors interpreted these figures as a reflection of differing transplant management; Spain has an opt-out scheme whereas Germany has an opt-in scheme. In some countries, living-donor transplants made up 100% of the total figure, whilst only 11 countries operate an active non-heart-beating-donor programme.

The Netherlands lead in KT activity, with 59.8 KT pmp, and the study has highlighted the need for leadership by the most active countries in organ donor management to assist in the implementation of similar strategies elsewhere in Europe.

Lower Urinary Tract Function: The Geriatric Perspective

OPTIMAL care of lower urinary tract (LUT) problems in the elderly population emerged as a central issue in an in-depth session at EAU16. A topic of wide scope, the lectures naturally ranged in focus, yet the overall message was clear: more research and more refined guidelines for treatment are necessary.

The severity of incontinence problems can be mediated by the maintenance of healthy practises in mid-life; however, age-related physical changes complicate matters from both the patient and physician's perspective. In terms of the patient, changes in metabolism, hormonal environment, morphology, and cerebral control can serve to compound the problem. In women, for example, childbirth or pelvic surgery may later lead to pelvic organ prolapse, a condition affecting approximately 50% of women >50 years old. For the physician, this complexity necessitates a comprehensive understanding of all the impacting factors, the interaction and outcome of which is difficult to control. Thus, "it could be that the next catch-phrase would be preventative geriatrics," said Prof Adrian Wagg, Chair in Health and Ageing, Medicine and Dentistry, University of Alberta, Edmonton, Canada.

Over 4,400 scientific pieces were displayed

Speakers cautioned against surgical treatment for LUT problems in older patients, particularly with regard to benign prostatic obstruction, as these patients are more vulnerable to post-surgery complications such as thromboembolism, loss of muscle mass, and blood pressure change.

Further obscuring the problem of optimal care of LUT problems in the elderly is the 'evidence-practice gap', as stated by Prof Wagg. The efficacy of antimuscarinic drugs in those aged 65–75 years has been supported by certain studies, and a Fit fOR The Aged Classification (FORTA) currently lists approximately 200 drugs in >20 therapeutic areas that are relevant to the elderly population. He added, "although we have more evidence, we need still more in older age groups, from pragmatic clinical trials. And we need to proactively seek treatment-related adverse events."

Statin Use May Reduce Prostate Cancer Patient Mortality

RESULTS of a comprehensive study including >30,000 patients from the Danish Cancer Registry suggest that the use of statins by prostate cancer (PCa) patients can lead to a reduction in mortality.

Recent studies have indicated that statins, which are commonly prescribed as a cholesterol-lowering medication, may have beneficial effects for PCa mortality. However, the results have remained inconclusive due to the risk of a type of sampling bias termed the 'healthy user bias', which refers to the risk that the group of statin users included in the study may be healthier than the control group. This study is unique in that its design allows control of this potential bias.

Lead researcher, Dr Signe Benzon Larsen, Danish Cancer Society, Copenhagen, Denmark, commented: "Several studies have shown an association between statin use and lower PCa mortality, but the exact relationship has been open to doubt. Due to the unique health care registries in Denmark, we were able to investigate the effect of statins both before and after PCa diagnosis and the effect of type and dose of statin use. This means that we have probably the most extensive data so far indicating that statin use is associated with improved mortality outcome."

The researchers identified all 31,790 Danish men diagnosed with PCa from 1997–2012, 6,675 of whom had used statins within 3 years prior to diagnosis, and 6,780 that had used statins after diagnosis. Results demonstrated that statin users have a reduction of around 19% in all-cause death, and a 17% reduction of PCa death, indicating that statin use lowers mortality in PCa patients.

Prof Bertrand Tombal, EAU Scientific Congress Committee, said: "Whilst awaiting the results of the ongoing trials, this study increases the evidence that statin use may be an easy add-on prescription to lower mortality from PCa. Given their excellent safety profile, their well-established benefit on metabolic syndrome, and their relatively low cost, statins are an option that should be discussed with our PCa patients."

Blood Test Enables Prediction of Prostate Cancer Aggressiveness Preoperatively

HYPOGONADISM, or low testosterone levels, may serve as an indicator of pathological stage of prostate cancer (PCa) in preoperative patients, following a simple blood test, according to a study presented at EAU16.

The Gleason pattern is a common measure of tumour severity in PCa patients; a score of 1 equates to normal cells in a tissue sample, and a score of 5 suggests near complete tissue cell takeover. PCa is the most common male cancer, and mortality is high in patients whose tumours show Gleason pattern 5. Research shows that hypogonadism and levels of sex-hormone-binding globulin can predict the severity of PCa prior to a radical prostatectomy (RP).

In a press release dated 12th March, Dr Marco Moschini, Department of Urology, San Raffaele Hospital, Milan, Italy stated that "there is an urgent need for new research to uncover the role which hormones play in prostate cancer development," while Prof Alexandre de la Taille, Chairman, Department of Urology, CHU Mondor, Assistance Publique des Hopitaux de Paris, Paris, France commented, "these cancers, developed in this special hormonal environment, are probably due to different molecular pathways and represent a new field to explore."

The study included 1,017 patients with no previous hormone treatment, undergoing RP at one institution. Serum hormone levels were measured the day before the surgery to define those with hypogonadism. In the retrospective analysis, 118 patients showed Gleason pattern 5; hormone levels were found to be independently associated with this score. Hypogonadism has been linked to higher rates of biochemical recurrence and an advanced pathological stage, and thus may serve to highlight postoperative risk in PCa patients.

"What we do not yet know is if this is an association, or if hypogonadism in some way increases the risk of developing high-grade prostate cancer. If this is the case, then it may be that treating the hypogonadism can lessen this risk, but we need more work before we can be sure of that" added Dr Marco Moschini.

Updates in Non-Muscle Invasive Bladder Cancer from EAU

SIGNIFICANT dialogue surrounded the topic of non-muscle invasive bladder cancer (NMIBC) during the EAU congress, specifically focussing on surveillance for upper tract urothelial carcinoma (UTUC). "The risk of UTUC in bladder cancer patients is a lifelong constant, and high-grade recommendations as to schedule, intensity, and duration of upper urinary tract (UUT) surveillance cannot be made at present," stated Dr Gianluca Giannarini, Urology Unit, Academic Medical Centre, Udine, Italy, in a thematic session in which the need for an increase in evidence-based guidelines in NMIBC was discussed.

"In terms of the evidence base, we only have retrospective, non-comparative, non-controlled cohort studies at our disposal. There have been a few surveillance protocols for UUT, but these are diverse, non-validated, and mainly stage-adapted" he added. This has left urologists with little to guide their surveillance of NMIBC: "We therefore have no high-grade recommendations on who to monitor, how to monitor, how often, or for how long patients should be monitored for UTUC."

The potential for a kidney-sparing surgical technique that could be used in place of radical nephroureterectomy was proposed by

Dr Sharokh Shariat, Department of Urology, Medical University of Vienna, Vienna, Austria.

Dr Shariat pointed out that in the case of small tumours there is still only the one option: removal of the kidney, and suggested that "at the moment, one size fits all and there is a serious risk of over-treatment." The various aspects of the kidney-sparing surgery were also scrutinised, including the safety and efficacy aspects, and the criteria for eligibility in patients. "The rationale for kidney-sparing surgery is clear, but I must disclose that data is currently weak. Ureteroscopy is useful for diagnosis, but there is a risk of delaying the definitive treatment."

Finally, Dr Shariat further recommended the use of digital ureteroscopy for optimal results. Whilst there is clearly still a long way to go in both surveillance and surgical techniques, the advent of new practices such as genomics are a step towards improved care.

Potential Mechanism Uncovered That Explains Correlation Between Sleep Apnoea and Poor Cancer Outcomes

HYPOXIA-related angiogenesis could represent the hidden mechanism behind increased cancer aggressiveness and mortality associated with sleep-disordered breathing (sleep apnoea), according to an animal study presented at EAU16.

Though the association between worse cancer outcomes and sleep apnoea remains cloaked in controversy, recent evidence has led to increased support for the idea. Intermittent hypoxia is one consequence of sleep apnoea, a condition that has also been linked to an increased risk of stroke and high blood pressure.

In a murine study, which included 24 mice, each mouse had a subcutaneous kidney tumour and was allocated to either the experimental (n=12) or the control group (n=12), researchers were able to demonstrate that intermittent hypoxia promotes the formation of blood vessels within tumours. It is thought that this effect is a result of increased production of vascular endothelial growth factor (VEGF).

In the study, mice in the experimental group were subjected to varying oxygen levels (mimicking intermittent hypoxia). The researchers noted an increase in vascular progenitor cells (6.1±0.76 versus 4.5±1.1, p=0.001) and endothelial cells (4.0±0.8 versus 2.5±1, p=0.013) within the tumours of mice who experienced intermittent hypoxia as compared with those in the control group. The researchers also observed an increase in circulating VEGF in the experimental group (306±93 versus 204±45 pg/mL, p=0.001); no significant difference was observed amongst other factors, such as tumour growth.

"Patients suffering from obstructive sleep apnoea usually suffer from intermittent hypoxia at night. This work shows that intermittent hypoxia has the potential to promote the formation of blood vessels within tumours, meaning that the tumours have access to more nutrients," explained Dr Antoni Vilaseca, Lead Researcher, Hospital Clinic De Barcelona, Barcelona, Spain in a press release dated 12th March.

Despite these thought-provoking results, the authors advise caution in the general interpretation; "This is of course an early animal study, so we need to be cautious in applying this to humans. Nevertheless, this work indicates a plausible mechanism for just why conditions, which restrict oxygen flow to tissues, like sleep apnoea, may promote cancers."

Frontiers of Prostate Cancer Care

OPTIMISED diagnosis and therapy for patients with prostate cancer (PCa) formed the thematic backbone of a stimulating series of debates, lectures, and a case discussion at EAU16.

Genetic research is proving highly influential in a range of therapeutic areas, and the same can certainly be said of PCa treatment optimisation. Molecular characteristics are able to indicate the rate of disease transition in individual patients; the work of Prof Thorsten Schlomm, Chief Physician, The Martini-Klinik, University Hospital Hamburg-Eppendorf, Hamburg, Germany, aims to champion this finding in PCa management. "In the future we will create a molecular speedometer for each patient in order to precisely predict individual patients' progress," he predicted.

Different perspectives on the role of magnetic resonance imaging (MRI) in PCa treatment provided an interesting insight into biopsy strategies. MRI is primarily used to localise index lesion, and was deemed most beneficial for clinical use in those undergoing re-biopsy. MRI/transrectal ultrasound fusion-guided biopsy was discussed as a technique to identify significant PCa minimal cores, and future research will need to explore how to sustain the cost-effectiveness of MRI technology.

Strong debate over the timing of radiotherapy after radical prostatectomy (RP) highlighed contradicting opinions. While some advocated for adjuvant radiotherapy, others argued that early salvage radiotherapy provides better optimisation of survival against adverse effects, and less overtreatment, with Prof Thomas Wiegel, Medical Director Department of Radiation Oncology, Universitätsklinkum Ulm, Germany insisting that there is no overtreatment from adjuvant radiotherapy after RP.

The relevance of classic hormone therapy to current chemotherapeutic approaches was also contended, although ultimately its uses were supported with the caveat that urologists need to be multidisciplinary in their care, and adapt to new technology. This sentiment was echoed in the humorous yet prescient tone of moderator Prof Kurt Miller, Chairman, Department of Urology, Benjamin Franklin Medical Center, Berlin, Germany, who remarked, "of all [the] inhabitants on the planet, none is more resistant to change than humans. Except urologists, of course."

Surveillance Allows Better Quality of Life Than Treatment in Low-Risk Prostate Cancer Patients

ACTIVE SURVEILLANCE could be the answer to improving the quality of life (QoL) in men with low-risk prostate cancer (PCa).

PCa is the most common male cancer in Europe, with nearly 400,000 new cases each year. Previously, patients were treated with either radical prostatectomy or radiotherapy. Increasingly, research suggests that for those with less aggressive cancers, monitoring of the cancer can be more effective for maintaining QoL.

One study presented at EAU16 compared 121 active surveillance patients with 74 treated with surgery and 232 treated with radiotherapy. The study included patients aged 66–69 years with low-risk PCa followed-up at Year 5 and 10. Two-hundred and four men who did not have PCa were also included for reference. QoL was assessed using the SF-12, EQ-VAS, STAI-6, and EPIC questionnaires.

The study found that patients on active surveillance had a QoL similar to those who did not have PCa, compared to those who underwent treatment. These patients reported better urinary function, less urinary incontinence, and better sexual function compared with men who underwent radical prostatectomy, and significantly better sexual satisfaction scores compared with the radiotherapy patients.

> “When choosing treatment, it is important that men think about the potential side effects that are related to immediate curative treatment, like becoming incontinent or losing the ability to have an erection. When considering active surveillance, they should try to imagine whether living with untreated cancer would cause any stress, or that the follow-up visits lead to stress instead of reassurance.”

Almost 17,000 tweets shared

The choice to have either treatment or active surveillance remains a difficult one.

Dr Lionne Venderbos, Department of Urology, Erasmus University Medical Centre, Rotterdam, Netherlands stated in an EAU press release dated 14th March 2016: “When choosing treatment, it is important that men think about the potential side effects that are related to immediate curative treatment, like becoming incontinent or losing the ability to have an erection. When considering active surveillance, they should try to imagine whether living with untreated cancer would cause any stress, or that the follow-up visits lead to stress instead of reassurance.”

This study gives rise to more options for patients with low-risk PCa, although more research is needed beyond questionnaires to elucidate all the risks and benefits of each option.

More Attention Must Be Paid to Complexity of Stone Disease

NUANCED differences in the detection, care, and management of stone disease emerged as a key point of discussion at the recent EAU16 congress. Although slight, these basic differences require shrewd attention in order to improve the prevention and treatment efforts of urologists, with the potential to significantly affect patient quality of life.

Mismatched perceptions of patients and doctors was said to lead to inappropriate and therefore unnecessary protocols for the treatment of stone disease patients. A refined understanding of the complexity of stone formers will further improve physician responses to pain symptoms, dietary needs, and therapeutic requirements. Although complex, this will be far simpler to navigate when armed with a more robust knowledge of the basics, such as urine analysis and relevant patient-specific dietary recommendations. This process can be improved with a metabolic evaluation that focusses on the basics, such as urinalysis, and individualised approaches; for example, a patient with cystine stones may benefit from a different dietary regime to one with uric acid stones.

"Stone formation is complex and we need a deep understanding of issues such as metabolic evaluation," said Prof Thomas Knoll, Department of Urology, Klinikum Sindelfingen-Böblingen, Sindelfingen, Germany. The need for proper urine collection is particularly important in this regard, and further basic recommendations were made at the talks, such as regular water consumption (2–2.5 L/day), limited sodium and calcium intake, and in some cases restricted oxalate and uricacid intake.

An important debate that related to these themes focussed on the proposed necessity of increased patient-specific care. Forming the essence of the debate, the notion of preventive treatment was posed in opposition to the opinion that increased fluid intake and endourological treatment alone is adequate, whilst also touching on the lack of scientific evidence and poor compliance to therapeutic strategies by patients.

Infertility Linked to Increased Risk of Metabolic Disease in Ageing Men

MEN with fertility problems are predisposed to an increased risk of metabolic disease as they age, according to research presented at EAU16.

Infertility affects approximately 15% of couples, and around half of these cases arise because of male infertility issues. In men with infertility issues, a reduction in life expectancy is also expected; this link has been demonstrated in men with low semen quality.

The reasons for the association have so far remained elusive, and no biochemical markers or prevention strategies have previously been developed.

However, a Swedish research group revealed that they have now measured sex hormone levels and other biochemical parameters in infertile men. The group compared 192 men with a low sperm count with 199 age-matched controls, looking at differences in sex hormone levels between the groups, along with other markers such as bone mineral density (which indicates osteoporosis risk) and HbA1c.

The researchers found that one-third of men under 50 years of age with fertility problems showed biochemical signs of hypogonadism; this is 7-times as common compared with control subjects. Infertile men also had low bone density, which was particularly prominent in men with low testosterone levels, indicating an increased risk of fractures and osteoporosis. Elevated glucose and HbA1c were also observed in hypogonadal men, indicating a predisposition towards diabetes.

Lead researcher Dr Aleksander Giwercman, Chairman, Reproductive Medicine Centre, Skåne University Hospital and Lund University, Malmö, Sweden, summarised in a press release dated 12th March: "We found that a significant proportion of men from infertile couples show biochemical signs of hypogonadism. This may be affecting their fertility, but they can also serve as early warning signs for metabolic diseases in later life, such as osteoporosis or diabetes. We would recommend that levels of reproductive hormones should be checked in all men seeking advice for fertility

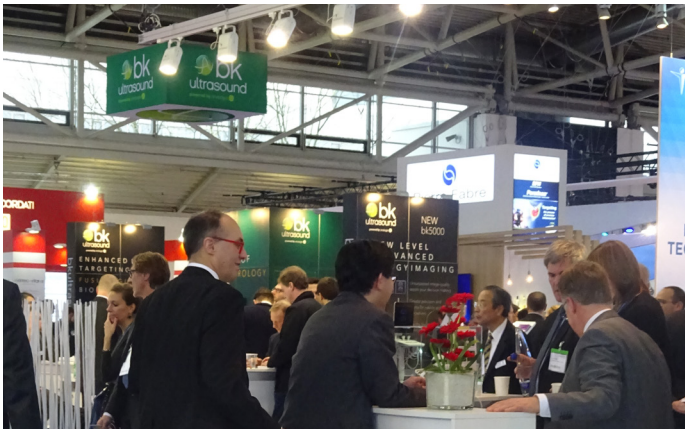
problems. Those at risk of serious disease should be followed after the completion of fertility treatment."

Erectile Dysfunction: An Update From EAU

ERECTILE dysfunction (ED), especially following radical prostatectomy was a topic of much discussion at EAU16. ED is a multifactorial condition that is associated with a number of psychological factors. Dr Giorgio Gandaglia, Resident, Department of Urology, Urological Research Institute, University Vita-Salute San Raffaele, Milan, Italy said, "up to 70% of patients still experience postoperative ED, even when a bilateral nerve-sparing approach is performed."

Various treatments are available for ED, though phosphodiesterase 5 (PDE5 inhibitors) are currently the most effective option. The current evidence for PDE5 inhibitors has arisen from a number of randomised controlled trials, though some concerns exist regarding the selection criteria, follow-up periods, and timing of drug administration within these trials. Dr Gandaglia stated: "A recent study showed that patients at immediate risk of ED after surgery are the ones who benefit most from the use of PDE5 inhibitors and they are the ones that should be targeted."

Some options for second and third-line treatments exist; however, these are more invasive than oral PDE5 inhibitors. Vacuum erection devices and intracorporeal injections are effective second-line therapies, whereas a penile prosthesis is the only effective third-line treatment in non-responders or in patients who do not comply with earlier treatment options.



One cause of ED is Peyronie's disease, which has both physical and psychological implications. Dr Evangelos Zacharakis, Consultant Urological Surgeon, Department of Urology, Guy's hospital, London, UK said: "There have been many oral treatments for Peyronie's disease, most of which are not effective, apart from pentoxifylline and L-arginine/PDE5 inhibitors. There is limited evidence that interferon and verapamil are effective, whereas the evidence for collagenase is Grade A/Level I."

The recommendations for surgery vary with the disease but Dr Zacharakis suggested that plication or Nesbit plication is available for deformities of <60°, while grafting by an experienced surgical team is possible for deformities of >60°. Many patients do not seek treatment due to embarrassment, with many ignoring milder symptoms.

Urological Infections and Their Treatment Requires Redefinition

ADVANCES in research that have highlighted room for improvement in terms of the management and treatment of urological infections were prevalent in discussions at EAU16. "It is high time to redefine urinary tract infections and urinary tract disorders based on routine test findings only," counselled Dr Vitaly Smelov, Postdoctoral Fellow, International Agency for Research on Cancer, World Health Organization, Lyon, France. New technology has identified a range of non-culturable bacteria present in urine, which have previously evaded detection in standard tests.

The cautious use of antibiotics in the treatment of urological infections was emphasised at the talk; with over 25,000 deaths per year

attributable to drug-resistant bacteria, and a 20–50% rate of unnecessary antibiotic prescription in the USA, stringent management of their use is well supported by the available data. This is particularly relevant in the case of hospital-acquired infections, which are largely antibiotic-resistant.

Past approaches to research were also redefined. "Once upon a time, the bug was the focus. That is history. The host susceptibility caused by genetic polymorphisms is now in the focus and we are just beginning to understand this interplay," stated Dr Björn Wullt, Consultant, Division of Microbiology, Immunology and Glycobiology, University of Lund, Lund, Sweden. Genetic mapping has great potential to explain host response downregulation and antibiotic resistance, and is thus of significance to therapeutic development.

Other data suggested that 30% of initial urinary catheterisations are unwarranted, indicating a need for better judgement of their use. Nuanced management of infection in neurogenic and non-neurogenic patients was discussed, along with the role of brush cells in the urinary tract. Overall, the meeting provided a comprehensive review of what appears to be a fresh slate in urological infection research for 2016.

More than 13,000 people

> "Once upon a time, the bug was the focus. That is history. The host susceptibility caused by genetic polymorphisms is now in the focus and we are just beginning to understand this interplay."

Did you miss to visit our booth at EAU 2016?

Take the opportunity to learn how our solutions could help answer three of the 'frequently asked' questions by your colleagues.

Q **How could we increase the diagnosis of prostate cancers while improving the quality of our Targeted biopsies?**

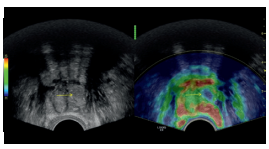
A Experience Volume Navigation. A Real Time, accurate, quick, easy to learn, fully integrated US/MRI fusion solution in our ultrasound devices. To help save costs, procedural time and space while improving your patient experience.

Q **What could be the value to have a tiny ultrasound device always available in our pocket?**

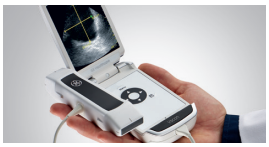
A Vscan™ with Dual Probe is the pocket-sized ultrasound delivering crisp images quickly and simply. With two transducers in the same probe, you get a device that helps improve your productivity and quality of patient care from superficial to deeper anatomies. You could have more information just adding visualization to your clinical examination and decide to send your patients for deeper investigations. Potentially changing your patients' management.

Q **Could I use Vscan to measure Urinary Bladder?**

A Vscan with Dual Probe can do much more than the simple measure of the bladder. It's a full pocket-sized ultrasound device that you can use to measure the bladder and also check the urinary jets for the assessment of potential ureteric obstruction.



Read the clinical case



Watch the product video

Watch the educational video to learn more

Imagination at work

Contact us

Editorial Board Interviews

Christopher Eden

Professor of Urology, The Royal Surrey County Hospital, Guildford, UK; Special Advisor to the National Institute for Health and Clinical Excellence; Medical Advisor to PCaSO Prostate Cancer Network.

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

A: As is often the case, I worked for a boss who inspired me. I was a Senior House Officer at the time and doing my first job in urology, having qualified as a doctor 3 years before. He took me aside and told me that I should consider urology as a specialty as it has a great breadth and not too much emergency operating! At that time, it was possible, and in many cases necessary, to treat the full range of urological pathology but subspecialisation has changed this; for the better, I might add.

Q: How much have our understanding and the treatment of prostate cancer (PCa) developed since you first began working in this field?

A: For such an important disease, PCa attracted surprisingly little basic science and clinical research until the last two decades. Since then it has changed greatly; we now have an enormous amount of work being done in every aspect of the disease: screening and diagnosis, surgery, radiotherapy, adjuvant therapy, focal treatment, and castrate-resistant disease. It is heartening to see an increasingly scientific basis for the advice we give our patients.

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

A: It is very rapid. The period 2000–2010 was the decade of laparoscopy, and 2010–2020 is going to be the decade of robotic surgery. It is important to realise, however, that not every country will be able to afford to have robots in their operating theatres, and that for these countries, laparoscopic surgery offers a very good alternative, which may not be inferior in expert hands.

Q: Are there any recent advances in technology that have had a significant positive impact on the management and treatment of urological conditions?

A: Too many to mention. The advent of the charge-coupled devices allowed us to stop operating with our eyes pressed up against endoscopes, which is safer from the infection control viewpoint, and more comfortable too. Laparoscopic and robotic surgery are two other obvious examples. Peel-apart sheaths for suprapubic catheter introduction, better stone baskets, finer ureteroscopes, and flexible instrumentation (I am showing my age here!) have all made life easier for the urologist and surgery safer for their patients.

Q: What do you think will be the 'next big thing' in laparoscopy, and how long do you imagine it will be before this is introduced into clinical routine?

A: Being able to fuse imaging from a magnetic resonance imaging, computed tomography, or ultrasound scan with the anatomical view in real time is something of a holy grail for laparoscopic and robotic oncological surgery. It will become a reality within the next 10 years but the concern is going to be expense, which at least initially, will limit its diffusion.

Q: The high cost of robot-assisted radical prostatectomy is a factor that reduces its accessibility to patients with PCa; how long do you think it will be until robotic technology becomes more cost effective?

A: As long as it takes for a competitor to emerge, probably from India or China. This would be really interesting and would have a profound impact.

Q: What do you think is the greatest challenge faced by urologists in Europe today, and how should it be combatted?

A: There are still so many unanswered questions in urology, especially in my particular field which is PCa. One of the most fundamental areas, and the one in which society can perhaps make the biggest impact on PCa mortality, would be to accept the lessons from the European Randomized Study of Screening for PCa. and to introduce them. Risk-adapted screening and better biomarkers will make this happen faster, both of which are around the corner even now.

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

A: Greater centralisation of complex surgery. The days of a surgeon 'doing his best' are over. Patients with complex and demanding medical needs deserve to be looked after by true experts.

Q: Are there any areas of development within the field of urology that are particularly interesting at the moment?

A: The areas where I am actively involved in research at the moment all relate to PCa: urinary biomarkers, focal therapy, adjuvant therapy for surgery in high-risk patients, and local treatment of oligometastatic disease.

Q: Could you tell us a little about your role with the National Institute for Health and Care Excellence (NICE)? How effective have NICE guidelines been in improving treatment for urological conditions in recent years?

A: NICE has had a major impact in the UK in standardising urological practice and effecting change where needed by highlighting the evidence in the literature. Due to its more UK-specific nature, it seems to have had an even greater impact on day-to-day practice than the European Association of Urology and American Urological Association guidelines.

Q: Do you have any advice for young doctors and practitioners hoping to start a career in urology?

A: Do it!

Selçuk Guven

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

Q: At what stage of your training did you decide to pursue a career in urology?

A: I think this choice comes down to each person's disposition. I myself did not initially plan to have an academic career. Early in my residency I noticed that I like to deal with details and that I love reaching the limits of the unknown in all kinds of information; my academic career began after these realisations.

Q: What inspired you to specialise in laparoscopy in particular?

A: In conjunction with technological advancements and the greater diligence they allow, endoscopic techniques and laparoscopy have replaced most open urological surgeries. I started my urology residency during a period in which these changes were fast occurring. In those days Turkish Urological

Laparoscopy (Turkurolap) training courses had only just started, and I was one of the lucky first applicant trainees. Turkurolap courses led to the widespread use of laparoscopy in my country. Our practice could not remain indifferent in the face of these new techniques. Like many of my friends, my colleagues and I came together and developed thanks to these courses.

Q: How effective do you consider Turkey's healthcare system to be? How does this system shape the relationship between urologists and their patients?

A: In 2003, Turkey made major changes to its healthcare system and the Health Transformation Programme was introduced. Universal health coverage may have brought some advantages for patients, yet it comes with its limitations for both patients and doctors. As with other healthcare providers, increased workload for health professionals, performance-related pay for health staff, and privatisation of healthcare have affected urologists. These limitations have also reflected negatively on scientific research as it is thought that research causes loss of time and money. Due to the impact on patients, doctors, and any third parties concerned, the system should be considered from different perspectives.

Q: What are the main issues that urologists face today?

A: The main issue is standardisation of urological education, diagnosis, and treatment for all people. Injustices between different departments in terms of the education of residents seem difficult to cope with. The lack of interest in some subspecialty areas such as reconstructive urology, along with overdiagnosis and overtreatment of urological diseases that will never be clinically significant, is problematic. Differences in urological healthcare quality between countries and regions also add to the issue.

Q: What new technologies are impacting day-to-day practice in urology? To what extent are they impacting the treatment of patients, and how?

A: There are important advancements in molecular research and engineering, thus clinical practice has changed rapidly in recent years. Newly discovered pathways and targets, developments in cytotoxic treatments for urological cancers, and evolving molecular imaging technologies have had an important impact on the treatment of both oncological and non-oncological urological diseases.

Q: Could you speculate on what developments you foresee in urology over the coming year?

A: I think the results of interdisciplinary research teams will have a significant role in the future development of the field.

Q: What research are you currently undertaking and where do you think it will lead?

A: I am currently working on prospective multicentre clinical studies concerning stone disease and molecular research at our research centre.

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: Translation of research to clinical practice for both diagnosis and treatment should be the centre of interest. I think this will be fruitful and enjoyable on both a global scale and a personal level.

Q: What advice would you give to someone who is interested in developing a career in urology?

A: After proper basic urology training the first step is to choose the field of specialisation he/she loves. Following this, it is important to improve surgical skills, writing skills, and knowledge of science as it relates to society.

> "Early in my residency I noticed that I like to deal with details and that I love reaching the limits of the unknown in all kinds of information; my academic career began after these realisations."

Riccardo Autorino

Associate Professor of Urology, University Hospitals Urology Institute, Case Medical Center, Cleveland, Ohio, USA.

Q: Why did you choose to specialise in urology during your medical training?

A: Urology was not my first option when I was finishing medical school and looking towards the next step in my early medical career. I was oriented towards a surgical specialty - my thesis was in the field of general surgery and I was serving as an intern in the General and Transplant Surgery Unit at my university hospital. During that experience I was exposed to kidney transplant surgery; being part of the transplant team was a great experience. At that time, a graduating medical student could apply to different types of residency programmes and like many of my colleagues that is exactly what I did. I was awarded a place on both the urology and general surgery programmes, and so at that point I had to choose. While my initial passion was for general surgery, I realised after speaking with more experienced colleagues that urology was the way to go as it offers a unique combination of clinical and surgical domains. Today, when I look at all the surgical specialities, I believe I made the right decision.

Q: You are involved in the subspecialties, robotic and minimally invasive surgery, both as a practitioner and in development of these techniques. How have these areas progressed in recent years, and where would you like your research in this area to lead?

A: The urological surgical field has witnessed a technological revolution since the introduction of laparoscopic and robotic techniques, as well as endourology. There has been tremendous progress in terms of the available instrumentation and technology, and surgical outcomes have ultimately been optimised. The idea behind minimally invasive surgery is to offer effective and safe procedures with the advantage of a faster recovery and less postoperative pain. Urology, more than other specialties, has embraced this idea and almost the entire spectrum of urologic disease, either benign or cancerous, can now be managed via a minimally invasive approach. I am sure that in the next decade we will witness further advances in this field. For example, we might have new robotic systems besides the well-established daVinci™ robot. At the same time, we will have new tools for surgical navigation, and we are going to optimise focal treatments for localised cancers. In other words, this is a very exciting era for those interested in minimally invasive surgery.

Q: Are there any other areas of urology research that you would like to become involved in?

A: Urological oncology is another exciting area of clinical research. For example, in the field of prostate cancer, novel biomarkers have become available and magnetic resonance imaging has gained ground over the past few years. In addition, the concept of active surveillance has now been largely adopted and the idea of focal therapy is appealing to many, despite the fact that it is still not ready for prime time. Making a difference to the lives of so many patients who will have to experience the terrible news of being diagnosed with a cancer is certainly extremely rewarding for any physician.

Q: How has the use of robotic surgery changed the training of doctors and surgeons?

A: In the era of open surgery, the paradigm in surgical training was quite straightforward: 'see one, do one, teach one'. The introduction of laparoscopy and, following this, robot-assisted laparoscopy, has dramatically changed the way trainees learn. A thorough understanding of the technology, including its uses and limitations, is critical to maximise patient outcomes and safety. Development of curricula for robotic surgery represents an area of ongoing discussion, and the

process of credentialing has received growing attention. Use of simulators has been implemented in teaching institutions worldwide as an additional step towards standardised structured training programmes. Recently, efforts have focussed on creating a standardised curriculum with competency-based assessments. An example of this approach is the ERUS (EAU Robotic Urology Section) Robotic Curriculum, and in this respect, scientific societies will play a key role in defining the standards of modern surgical training.

Q: You have worked in both Italy and the USA. What are the main differences that you have observed within their healthcare systems, in terms of both doctors and patients?

A: A few words are certainly not enough to explain how the American health system is unique and different compared with the Italian health system, or any other system in industrialised democracies. I am currently enrolled in a master's degree programme in healthcare management, as one of my goals is to better understand this system and its controversies. During our first semester, we read a book entitled 'The healing of America' by T.R. Reid. This is a very easy but, at the same time, incredibly informative read that I would highly recommend to those interested in this topic. As a physician who received most of his training in Europe, some features of the US system, such as the business-oriented mindset and the lack of universal coverage, are quite questionable. On the other hand, I can appreciate other positive aspects, such as the easier access to available resources and the continuous willingness to move forward. Having said that, the main actors on the stage, doctors (and healthcare providers in general) and patients, in the USA and Italy (or Europe), share common aims, expectations, concerns, needs, and hopes.

> "Another area that currently faces a number of challenges (especially in the USA) comes from the medico-legal risks of our profession, especially for those performing surgical procedures."

Q: What major developments do you foresee in the field of urology in 2016?

A: As already mentioned, urology as a specialty is always moving forward. It is our responsibility to stay tuned, and to catch upcoming discoveries and novelties; from nanotechnology and image guided and robotic surgery, to genomics and proteomics as well as tissue engineering and the many other groundbreaking innovations, this specialty will represent, once again, one of the most fascinating areas of medicine.

Q: What are the biggest issues facing urologists at the moment?

A: We were discussing the growing role of technology within this specialty. The downside is obviously represented by the increased costs associated with the development and implementation of this technology in an era where cost containment dominates the healthcare debate. Another area that currently faces a number of challenges (especially in the USA) comes from the medico-legal risks of our profession, especially for those performing surgical procedures. Physicians are increasingly under pressure for these issues and this is certainly influencing the way we practice today.

Q: You have previously written about the relatively low number of abstracts submitted at congress that ultimately progress to publication, do you think that there is still a discrepancy in this area?

A: I do not have any recent data about this, but I expect there is. When I looked at this intriguing topic a few years ago, it was interesting to find out that only half of the studies presented in abstract form at major meetings such as the EAU and American Urological Association congresses are ultimately published as full length manuscripts in peer-reviewed journals. Others have looked at the reasons as to why this happens, and they have found that lack of time represents the top reason for researchers not to pursue the publication of their work. Certainly, it is one thing to have an abstract accepted in a meeting, but another to submit your own work for peer-reviewed publication.

In this respect, the commitment, energy, and enthusiasm of younger colleagues, especially residents and fellows, is often a key factor and it is the responsibility of more experienced colleagues to support and guide them in this challenging task.

Q: Will you be attending the EAU congress this year? How do events like EAU help urologists, like yourself, to develop their practice?

A: Yes, I will certainly be in Munich for the 2016 EAU meeting. This is a unique opportunity for networking, meeting old friends and colleagues, and establishing new collaborations. In addition, nowadays the EAU congress is second to none in terms of the scientific level of the meeting programme, as guests can attend multiple sessions on a variety of topics where the latest developments in the field are presented and critically discussed. I remember attending my first EAU meeting in Brussels; it was the year 2000 and since then I have only missed this key urological event a couple of times. The EAU meeting is an experience not to miss, either as a young resident or as an experienced attending physician.

Q: What advice would you give to medical students who would like to follow a career in urology?

A: Choosing the right medical specialty probably represents the most important decision for a young graduating doctor. I would say that if one is inclined towards a particular surgical specialty, then urology should be on top of the list, for several reasons. First, this specialty offers a unique mix of clinical and surgical endeavours. Second, the modern urologist can count on a large armamentarium of minimally invasive tools that are exciting to use. Third, urology is continuously evolving in the pursuit of superior outcomes for our patients. This translates into countless opportunities for scientific research. Last, but not least, urologists are nice people to hang out with.

Riccardo Bartoletti

Associate Professor of Urology, Department of Translational Research and New Technologies, University of Pisa, Pisa, Italy.

Q: Why did you decide to follow a career in urology?

A: I decided to become a surgeon during my time as a medical student. Surgery is a discipline that is able to provide immediate relief to the patient and a quick recovery from the disease overall compared with the 'medical therapy'. Moreover, for the surgeon, there is the additional challenge of attaining a perfect knowledge of surgical anatomy and physiology.

Urology was, at the time, a relatively 'young' specialty, although some descriptions of urological procedures date back to Ancient Egypt. Urology as a discipline mainly developed during the mid-20th Century, from which time it has been progressively changed and modernised. In the era of open surgery, urology was considered to be difficult to learn and practice due to the anatomical placement of different organs, such as the kidney, bladder, and prostate. These organs, all located within 'bone protected' sites, represented difficult sites for less experienced surgeons to access. At that time the Chief Professor within the University of Florence's Department of Urology, Alfiero Costantini, was considered by many to be a great 'urology master', an expert of urological practice; being admitted to this department was, for a young medical doctor, a point of honour and pride.

> "Over the last few years, novel methods for the prevention and diagnosis of urological cancers have been developed by the urological community."

Urology as a discipline has changed substantially since then; it includes multidisciplinary aspects and in many cases experience in subspecialties is strongly requested from the patient population.

Q: What issues most affect urologists and their patients currently? How can we best resolve these issues?

A: Urology as a medical discipline includes topics of relevant social interest, such as urinary incontinence, urinary stones, erectile dysfunction, and urinary infections. Many young urologists are preferentially oriented toward the treatment of urological tumours; thus other diseases of urological interest appear to be undervalued. This phenomenon is probably due to the spread of minimally invasive surgery; robot-assisted laparoscopic surgery in particular. Many urologists find approaches to major surgery using these new and 'easy-to-learn' technologies exciting and scientifically stimulating, although increased adaptability on the part of the surgeon will be required to successfully navigate between minimally invasive and open surgeries. At the same time, these urologists may struggle when faced with a situation requiring a quick changeover between minimally invasive and open surgery techniques.

Over the last few years, novel methods for the prevention and diagnosis of urological cancers have been developed by the urological community. This implies an increased risk of overdiagnosis and overtreatment, mainly for prostate cancer (PCa). Some of these aspects should be improved through accurate patient selection and the promise of upcoming basic research in the field. Greater attention should be given to those urological diseases previously described that are considered to be socially relevant.

Q: You have had an extremely varied career in terms of research, surgical advancement, and general practice; how do you think this has impacted your work and what aspects are you most proud of?

A: Those working during the innovative 'PC era' participated in the urology modernisation process, which included the development of new technologies, different approaches to patient care, and novel surgical techniques. Since that period I have strongly supported the need for pragmatic organisation and planning of daily activities. Both medical meetings and continuous medical education methods should represent the basis for new ideas to be employed in all research fields and daily clinical practice. This provides the correct environment for young urologists hoping to improve their skills and decision-making.

Q: How do you think the Italian healthcare system compares with systems in other European countries, as well as the wider world?

A: The current Italian healthcare system is incomparable with those of other European countries or the wider world; it is close to collapse due to several financial limitations, including the limited availability of technological innovations and the uncontrolled division of available resources. There are consistent differences between the North and the South of Italy in terms of both the quality of assistance for in and outpatients, and the academic and professional education of medical doctors.

Q: Do you feel that congresses such as EAU provide useful information for your day-to-day practice and affect the way that you, and others, treat urological conditions?

A: Yes, I do. The EAU annual congress provides useful information for the urologist and her/his daily clinical practice.

Q: You have presented work at the EAU congress in the past; to what extent do you think this helps to inform other urologists in their work and research?

A: Poster presentations may be useful to stimulate new ideas in urological research, whilst the main sessions may indicate appropriate solutions to treat urological conditions. Young urologists may also have the option of specific courses on the more relevant topics of urology, along with the opportunity to improve their surgical skills through hands-on sessions.

Q: What were the biggest developments in treatments that you saw at EAU 2016, and when do you think they will be available in the clinic?

A: The EAU Congress, recently held in Munich, indicated some significant innovations in each subspecialty of urology. In particular, some issues regarding PCa diagnosis and treatment have been discussed, as well as the need for antibiotic stewardship for the treatment of urinary infections. The joint meetings of different EAU sections highlighted the need for multidisciplinary teams in the treatment of urological cancers, the role of genetics in the management of infertile couples, and the need for a well-planned strategy in the treatment of urinary stones, which include accurate imaging studies and recurrent prophylaxis based on well planned metabolic evaluation. All clinical activities should be performed according to the EAU Guidelines to obtain evidence-based results, except for those patients who need tailored care and thus justify deviation from care standards.

Q: Where do you hope the field will be progressed to in 10 years' time?

A: My hope is to reduce the need of invasive treatments such as invasive surgery by utilising the advantages of minimally invasive strategies, and to encourage the evolution of natural medical therapies with evidence-based efficacy, which will reduce costs and toxicity. Moreover, the identification of alterations to the genome and/or microbiome will lead to the clarification of cancer genesis and development and the efficient use of predictive medicine.

Q: Are there any new areas of research within the field that you would like to become involved in now or in the future?

A: My new research includes PCa metabolism studies, the potential re-use of healthy tissues removed during surgical procedures for human-to-human transplantation, and focal treatments for PCa.

Q: What advice would you give to a medical student who is interested in pursuing a career in urology?

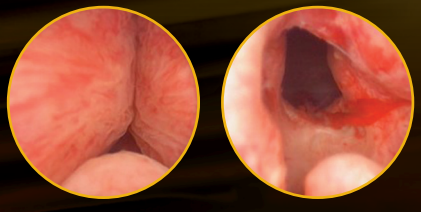
A: The first is to acquire clinical experiences in all the fields of the specialty by varying working groups, and both listening to and developing different points of view on each topic. Thereafter they should aim to choose a urological topic of personal interest in order to choose their subspecialty. This may lead to a deeper involvement in specific studies and a position of international representation as an opinion leader. International visibility represents, in my opinion, one of the strongest pathways to success.

UROLIFT®
BPH Relief. In Sight.™

UROLIFT® IS CHANGING THE GAME

BPH SYMPTOM RELIEF BACKED BY STRONG CLINICAL DATA

- 16 peer-reviewed publications, including 2 randomized studies
- Rapid and significant relief in AUASI, Qmax and QoL[1,3]
- Excellent safety profile
- Preservation of sexual function[2]
- Typically no catheter required after treatment[3]
- 3 years of published data[4]
- NICE recommendation based on independent meta-analysis



Pre-procedure *Post-procedure*

Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

IMPROVE YOUR BPH GAME TODAY. Check out the data and learn more at **UroLift.com**

Follow us on **@UroLift**

neotract®

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
4. Roehrborn, et al., Can J Urol. 2015 Three year results of the prostatic urethral L.I.F.T. Study

MANAGING PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CANCER: OLD DISEASE, NEW IDEAS

This symposium took place on 12th March 2016 as part of the European Association of Urology Congress 2016 in Munich, Germany

Chairperson

Per-Uno Malmström[1]

Speakers

Marko Babjuk,[2] Carsten Ohlmann,[3] Bernard Malavaud,[4] Ashish Kamat[5]

1. Department of Urology, Akademiska Sjukhuset, Uppsala University Hospital, Uppsala, Sweden
2. Department of Urology, Hospital Motol and 2nd Faculty of Medicine, Charles University, Prague, Czech Republic
3. Saarland University Medical Center, Hamburg, Germany
4. Department of Onco-Urology, Institut Universitaire du Cancer, Toulouse, France
5. University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Disclosure: Per-Uno Malmström has served on advisory boards and as a scientific advisor for Photocure AS. Marko Babjuk has recieved speaker's fees/honoraria from Astellas and Medac. Carsten Ohlmann has recieved speaker's fees/honoraria from Medac, has served on advisory boards for Medac, and was an invited lecturer for EAU. Bernard Malavaud is on an advisory board for Olympus. Ashish Kamat has served as a consultant or advisor for Abbott Molecular, Theralase, Telesta Therapeutics Inc. (formerly Bioniche), Sanofi, Oncogenix, Spectrum Pharmaceuticals, Merck, Heat Biologics, and Photocure, as a meeting participant or lecturer for Photocure, Sanofi, and Pacific Edge Ltd., and in a scientific study or trial for Merck, Heat Biologics, Photocure, and FKD.
Acknowledgements: Writing assistance was provided by Dr Tom Priddle, ApotheCom.
Support: Medical writing assistance was funded by MEDAC. The views and opinions expressed are those of the authors as expressed during the symposium and not necessarily those of MEDAC.
Citation: EMJ Urol. 2016;4[1]:36-43.

MEETING SUMMARY

Prof Per-Uno Malmström opened this symposium on non-muscle invasive bladder cancer (NMIBC) by describing the medical and economic burden caused by the increasing incidence of bladder cancer and the lack of new therapeutic options available to address the challenges of the management of NMIBC. Prof Marko Babjuk followed with a presentation that demonstrated that risk stratification using European Organisation for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) risk scores remains a useful tool for determining the best individual treatment options for patients. The next presentation, given by Dr Carsten Ohlmann, described the use of mitomycin C (MMC) for low and intermediate-risk patients as per the European Association of Urology (EAU) guidelines. However, despite a favourable safety profile, single case reports of severe adverse events following treatment with MMC should not be dismissed. MMC should therefore be given with care, with an emphasis on performing high quality transurethral resection of the bladder (TURB). Prof Bernard Malavaud then presented details of newer diagnostic methods, such as photodynamic diagnosis (PDD) and narrow band imaging (NBI), which offer better optical tumour recognition for the surgeon than the old standard of white light cystoscopy. The uptake of PDD and NBI in the future will facilitate an increase in the quality of TURB. Finally, Prof Ashish Kamat explained that recurrence of bladder cancer after bacillus Calmette–Guérin (BCG) treatment ('BCG failure') needs to be more clearly defined and stratified. He stated that optimal recognition of timing with relation to BCG immunotherapy is critical to determine the next steps. For example, in the past, patients with late recurrence who may have benefitted from challenge with BCG may have been overlooked.

Introduction

Professor Per-Uno Malmström

Prof Malmström welcomed the audience to the MEDAC-sponsored satellite symposium on NMIBC. Based on the results of interactive polling, 51% of the audience worked in a university hospital, 24% in a regional/local hospital, and 25% in a private office/hospital. Sixty-two percent of participants knew their hospital's recurrence rate after TURB: this was 26–50% for the majority (61%) of respondents. The audience voted on treatment options for two case studies at both the beginning and end of the symposium.

The Changing Epidemiology of Bladder Cancer

Professor Per-Uno Malmström

There are approximately 120,000 new cases of bladder cancer and 40,000 deaths per year in the European Union. Disease rates have been rising steadily in both males and females since the 1960s due to the increasing numbers of elderly people in the general population. Data from the Swedish National Registry shows an increase in non-invasive papillary carcinoma (Ta) tumours with a slight decrease in T2–T4 tumours, whereas in the USA there has been a dramatic increase in Ta tumours among the oldest age strata. Over a 5-year follow-up period, a 48% recurrence rate was seen in Sweden, mainly occurring during the first year, with a progression rate of 8%. Further data from the Swedish National Registry shows that bladder cancer survival rates remained largely unchanged between 1997 and 2011 in contrast to colorectal cancer survival rates, which increased over the same period. Bladder cancer represents 5% of total cancer healthcare costs, and productivity losses and informal care represent 23% and 18% of bladder cancer costs, respectively.[1] In summary, the current challenges in the management of NMIBC are: the rising incidence, especially among the elderly, the unacceptably high recurrence and progression rates, the static survival rates, and a lack of new drugs.

Case Study 1

Q1) How would you manage a 60-year-old female with a history of Ta low-grade, now presenting with multiple recurrent tumours at follow-up white light cystoscopy? You think she would not accept coagulation in the office. What would you do?

1. TURB in white light
2. TURB in blue light
3. TURB with NBI

Results of the voting at the beginning and at the end of the symposium are shown in Figure 1.

Q2) Do you give single-shot postoperative chemotherapy after uncomplicated resection?

1. Yes
2. No

72% of the audience voted yes.

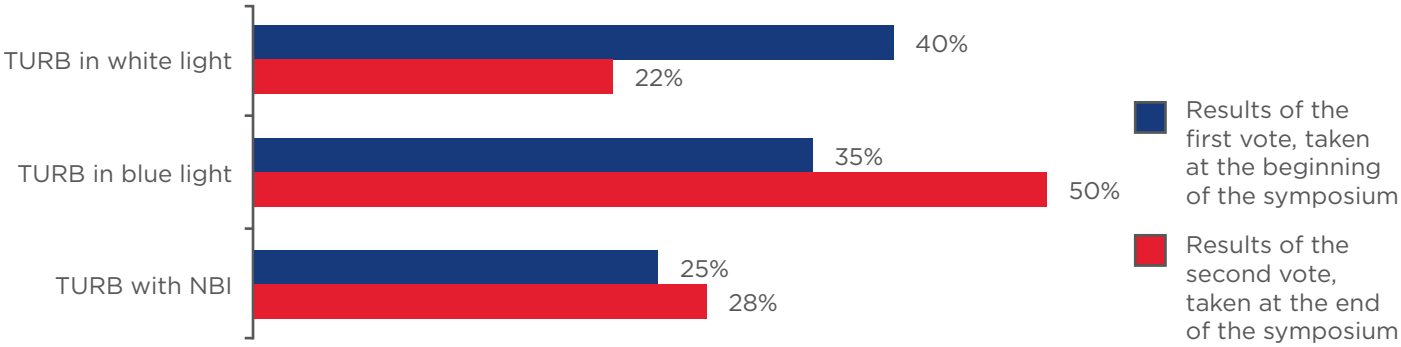


Figure 1: Results of questionnaire (question 1, case study 1); vote taken at the start and again at the end of the symposium.

The speakers posed the question "how would you manage a 60-year-old female with a history of Ta low-grade, now presenting with multiple recurrent tumours at follow-up white light cystoscopy? You think she would not accept coagulation in the office. What would you do?"

TURB: transurethral resection of the bladder; NBI: narrow band imaging.

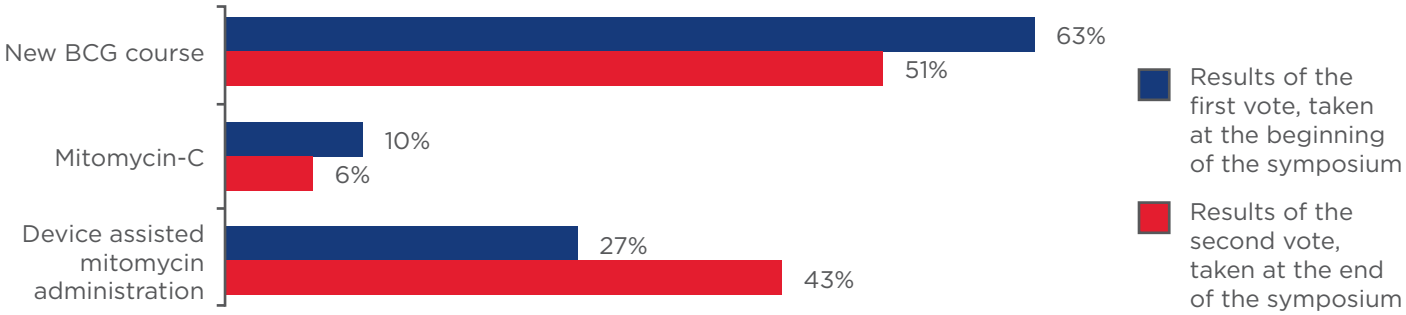


Figure 2: Results of questionnaire (question 3, case study 2); vote taken at the start and again at the end of the symposium.

The speakers posed the question "how would you manage a 71-year-old male, T1 high-grade, diagnosed 3 years ago? He completed 2 years of BCG and had a good result. Now cystoscopy shows a red area and the biopsy shows carcinoma *in situ*. You recommend cystectomy but he has a cardiac condition and he is very negative to major operations. Which of the alternatives do you suggest?"

BCG: bacillus Calmette–Guérin.

Case Study 2

Q3) How would you manage a 71-year-old male, T1 high-grade, diagnosed 3 years ago? He completed 2 years of BCG and had a good result. Now cystoscopy shows a red area and the biopsy shows carcinoma *in situ* (CIS). You recommend cystectomy but he has a cardiac condition and he is very negative to major operations. Which of the alternatives do you suggest?

1. New BCG course
2. MMC
3. Device-assisted mitomycin administration

Results of the voting at the beginning and at the end of the symposium are shown in Figure 2.

Do We Have Tools for Individualised Patient Treatment in Intermediate-Risk Non-Muscle Invasive Bladder Cancer?

Professor Marko Babjuk

When considering the treatment options for a 60-year-old female with multiple small papillary tumours on a control cystoscopy with a history of Ta low-grade tumour, there are three critical treatment steps that must be discussed: 1) endoscopic surgery, 2) early instillations of chemotherapy, and 3) further instillations. This session covered the first and third options. The EAU guidelines state that "In patients with a history of small, Ta low-grade (LG/G1) tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option." However, as not all tumours are suitable candidates and as this is not routine practice in many countries, TURB using endoscopy under anaesthetic should be considered. The goal is complete removal of all lesions and a reliable diagnosis based on pathology. Newer imaging techniques such as PDD can increase the visibility and reduce the risk of missing small recurrences. Data published several years ago showed pronounced benefits in patients with multiple lesions and recurrent tumours using TURB with fluorescence cystoscopy compared with white light cystoscopy.[2]

A meta-analysis of Hexvix® stratified according to risk group showed a lower risk of recurrence in the intermediate-risk group, together with a less pronounced, but still significant, benefit of PDD than in the high or low-risk groups.[3] NBI is another promising technique, albeit one with a paucity of published data at this time.

For patients with intermediate-risk tumours (with or without immediate instillation), guidelines state that: "1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6, and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality".[4] However, the question remains as to whether BCG or chemotherapy is the better option. This question was addressed in the FinnBladder I study,[5] a

20-year follow-up of 89 patients with NMIBC (highly recurrent disease, mostly Ta and G1 tumours). Of the patients treated with MMC, 80% experienced recurrence, compared with 59.1% of those treated with BCG. There was no significant difference in progression and survival. A meta-analysis of 2,820 patients (74% intermediate-risk) with a 4.4-year follow-up demonstrated that there was a 32% reduction in the risk of recurrence with BCG, although MMC was better than BCG without maintenance.[6] Once again, there was no significant difference in progression and survival. It is important to remember that BCG has a greater side-effect burden and owing to shortages is unavailable in many countries. In view of this, strategies to inform individual decision-making are highly desirable. Some promising work on genetic markers has been completed,[7] but this has yet to reach the clinic. The EORTC calculator, based on patients not taking BCG therapy, enables physicians to estimate the risk of tumour recurrence and progression on the basis of a number of clinical variables: number of tumours; tumour size; prior recurrence rate; T category; CIS; and grade.[8] In a patient with multiple recurrent small papillary tumours, this translates to a 62–78% risk of recurrence and a 6% risk of progression at 5 years. If the tumours are >3 cm, the risk of progression increases to 17%, placing the patient in the high-risk category. This shows that in patients with intermediate-risk tumours (in contrast with high-risk), recurrence appears to be a greater problem than progression.

The CUETO scoring model, which assesses patients treated with BCG, calculates a risk of tumour recurrence that is approximately 10% lower for intermediate-risk patients compared with those not receiving BCG therapy.[9] A more recent algorithm recommends a sub-stratification of intermediate-risk patients by individual risk factors to provide a more personalised approach.[10] For instance, using this approach, an intermediate-risk patient with large and/or multiple tumours that recur frequently should be considered as a high-risk case.

In conclusion, individual decisions can be made at almost all stages of treatment with intermediate-risk tumours; the quality of surgery is crucial and individual selection of intravesical treatment can be made using risk calculators.

Single Immediate Instillation of Chemotherapy After Transurethral Resection of the Bladder: Still a Valid Recommendation?

Doctor Carsten Ohlmann

Single instillation therapy is often recommended after white light TURB since, in some cases, there may be a small residual tumour or small tumours in other areas of the bladder, and there may be floating tumour cells that could re-adhere to the bladder mucosa, giving rise to additional papillary tumours. The EAU guidelines of 2009 recommended immediate instillation in all NMIBC patients (low-risk, intermediate-risk [plus 1 year of BCG], and high-risk [plus 1 year of BCG]).[11] These guidelines were based mainly on a meta-analysis published in 2004, which showed significant reductions in the risk of recurrence when using single immediate instillation (epirubicin, MMC, and pirarubicin).[12] Single immediate instillation was shown to be beneficial in patients with single tumours (risk of recurrence was reduced by 11.3%) as well as those with multiple tumours (risk of recurrence was reduced by 16.3%), although additional adjuvant instillation therapy was also recommended owing to the high recurrence rate (65.2%).[12] The current EAU guidelines now recommend immediate instillation therapy for low-risk and intermediate-risk patients only (plus 1 year of BCG or chemotherapy for intermediate-risk); no recommendation is made for high-risk patients.[13] The lack of recommendation in high-risk patients is based on data that suggest that single instillation therapy is most effective in patients with single primary or small tumours, and patients with an EORTC risk score of >3 did not benefit from single immediate instillation of epirubicin.[14] These findings were supported by a recent meta-analysis that also showed that single immediate instillation improves time to recurrence but not time-to-progression.[15] Furthermore, patients with a low risk of recurrence (EORTC score 0) showed the greatest benefit from single immediate instillation therapy.[15] There are some data showing a significant proportion of bladder perforation after TURB in patients who receive single immediate postoperative instillation therapy[16,17] and in these patients there is evidence to suggest a higher rate of recurrence[18] and a reduction in survival.[15]

In summary, the benefits of single immediate instillation therapy may have been overestimated

in the past. Nevertheless, there are subgroups of patients who will benefit from single immediate instillation therapy, namely patients with single primary tumours and those with smaller tumours, but the issue of bladder perforation and related complications should be considered. In the future, improved TURB techniques and instillation therapies will reduce the use of single immediate instillation therapy.

Can New Imaging Techniques Improve Diagnosis and Follow-Up?

Professor Bernard Malavaud

At present, there are two main imaging systems for increasing the contrast between the cancer tissue and the surrounding normal tissues. One of those is PDD, which relies on highlighting deficiencies in haem synthesis, namely a cancer cell's inability to metabolise hexaminolevulinate; this leads to an accumulation of protoporphyrin IX in cancer cells and causes the epithelium to become highly fluorescent. The other is NBI, which highlights microvasculature and the thickness of the mucosa using blue and green wavelengths of light. PDD enhances and facilitates the detection of papillary and flat high-grade lesions and a systematic review showed an increase in detection of 40% in CIS when using PDD.[19] White light imaging (WLI) visualises all layers of the bladder wall and relies on the physician's expertise in identifying variation in colour, contrast, and architecture, whereas PDD highlights cancer with a characteristic pink fluorescence. NBI relies on tumour angiogenesis;[20] the green wavelength of light highlights the larger vessels and the blue wavelength highlights smaller vessels. CIS has a characteristic vascular pattern with a 10-fold increase in microvascular density easily detected by NBI. A further benefit of NBI is that the red light scattering that causes blurring in WLI is completely absent. However, red light is introduced in digital post-processing to enhance contrast in the image. A comparison of bladder imaging techniques is given in Table 1.

A meta-analysis of 15 randomised controlled trials comparing WLI with PDD (n=11) and NBI (n=4) shows that there is a significant advantage in prevention of recurrence with both of the newer techniques (p=0.09 between subgroups).[21] However, there was no impact on rates of progression with either new technique.[21]

Taking the example of case number 2 described previously, a 71-year-old male with a flat lesion at follow-up and a malignant cytology, it is necessary to exclude a tumour in the upper tract using computed tomography urography, a tumour in the prostatic urethra using a biopsy, and CIS in the bladder using random biopsies or PDD. The National Institute for Health Care and Excellence guidelines suggest offering white-light-guided TURB with one of either PDD, NBI, cytology, or a urinary biomarker test to such a case.[22]

Table 1: Comparison of bladder imaging techniques.

Technology	Mucosal layer	Rationale	Physics	Characteristics
WLI	All layers		Variations in colour, contrast, and architecture	As per physician's experience
5-ALA/HAL PDD	Epithelium	Defective haem synthesis	Accumulation of PPIX	Pink signal, sharp and fragile for CIS
NBI	Submucosal vessels	Tumour angiogenesis[20]	Absorption by haemoglobin of the blue wavelengths of the visible spectrum	Increased density, tortuosity, and disorganisation
NBI	Mucosa	Increased number of cell layers (>10) WHO classification	Scattering of red light added by the system to reinforce contrasts	Reddish and indistinct appearance of the mucosa

5-ALA: 5-aminolevulinic acid; CIS: carcinoma *in situ*; HAL: hexaminolevulinate; NBI: narrow band imaging; PDD: photodynamic diagnosis; PPIX: protoporphyrin IX; WHO: World Health Organization; WLI: white light imaging.

In conclusion, new imaging techniques can improve diagnosis and follow-up. Both PDD and NBI are superior to WLI at the time of TURB and there is currently stronger evidence for PDD in the detection of CIS.

Bacillus Calmette–Guérin Failure: New Standardised Definition and Treatment Alternatives

Professor Ashish Kamat

Due to variations in endpoints and a lack of consensus on definitions of recurrence and/or progression of NMIBC, it is difficult to establish which treatments for bladder cancer are truly effective. A unified definition of BCG response and failure, with special attention to timing of the assessment, is therefore necessary to enable physicians and regulatory authorities to make informed decisions. For example, the landmark study of BCG by Lamm et al.[23] showed a comparable complete response (CR) rate at 6 weeks in both the induction and maintenance therapy arms (58% and 55%, respectively). However, after 6 months of observation the CR rate in the induction-only arm increased to 69%, whereas in patients who had received an additional 3 weeks of maintenance treatment the CR rate increased to 84%. Taken together, these results suggest that of the patients who would have been considered 'failures' at 6 weeks, 64% could have been salvaged with an additional 3 weeks of BCG therapy. This is especially important in the context of clinical trials that report results after 6 weeks. These data also, incidentally, demonstrate that maintenance therapy is most beneficial with the following protocol: a 6-week induction followed by 3 weeks of maintenance at 3 months, 6 months, and every 6 months thereafter (known as the SWOG protocol). Other maintenance protocols, such as one instillation every 3 months or one instillation every month, fail to show a benefit[24] and their use may represent one of the most common 'errors' in urology. In light of this, a definition of BCG failure must include a clear definition of adequate prior BCG therapy, namely BCG induction of 6 weeks plus at least one maintenance course of BCG of 3 weeks.[25] Furthermore, BCG failure must be assessed at the 6-month time point after the diagnosis of a high-risk tumour, as continuing unsuccessful therapy after this point will expose the patient to unnecessary risks. A white paper seeking to unify definitions, end points, and clinical trial designs for NMIBC has recently been published.[26] The term 'BCG unresponsive' has been adopted by the US Food and Drug Administration (FDA) and other agencies involved in clinical trial design. A BCG unresponsive patient is any patient with persistent high-grade disease at 6 months despite adequate BCG treatment, (including stage/grade progression at 3 months after instillation of BCG) or any patient with recurrence of high-grade disease within 6 months of last exposure to BCG (e.g. those on maintenance therapy). In order to provide consensus benchmarks for single arm studies, the following has been proposed by the International Bladder Cancer Group as evidence of 'clinically meaningful benefit': for BCG unresponsive CIS, an initial CR of 50% at 6 months; durable response rate of at least 30% at 12 months and 25% at 18 months; and for BCG unresponsive papillary disease, a recurrence-free rate of 30% at 12 months and 25% at 18 months.[26]

Radical cystectomy is the treatment recommendation for BCG unresponsive disease.[4] However, not all patients are candidates for surgery and further options may be necessary. One option is repeated BCG; however, after two or more failed BCG courses the number of metastatic and invasive cancers overtakes the number of patients who are tumour free.[27] A more recent study demonstrates that 71% of patients who have recurred with T1 disease while receiving repeated BCG therapy will progress to T2 disease, and almost half will be dead at 5 years.[28] BCG plus interferon (INF)-α may be a useful option in patients slower to fail BCG therapy; response rates when using this treatment were similar in BCG-naïve patients and patients who had failed BCG exposure >1 year earlier.[29] A study of BCG versus IFN-α2b plus epirubicin has shown that patients who have failed chemotherapy and then receive BCG can be salvaged more often than those who failed an initial course of immunotherapy.[30] An open-label, Phase II trial of intravesical mycobacterium cell wall DNA complex achieved significant activity in high-risk NMIBC patients who were BCG unresponsive or in those whom BCG treatment failed, especially those with papillary-only tumours (61%, 1-year disease-free survival rate).[31] Valrubicin is the only approved drug in the USA following BCG failure and shows a modest CR at 6 months of 18%.[32] Gemcitabine after BCG showed promising early response rates ranging from 39–50% but the majority of patients recurred at 1 year, with a 1-year recurrence-free

survival of 21%.[33] Similar recurrence-free survival rates of 27.6% at 1 year and 21.0% at 2 years were seen in a SWOG protocol-based study of high-risk patients.[34] Hyperthermic MMC post-BCG has shown demonstrable efficacy in a study of 111 patients with recurrent papillary NMIBC after BCG, with high disease-free survival estimates reported at 85% and 56% at 1 and 2 years, respectively; however, only 38% of patients were in the high-risk category and only 17% of patients had relapsed within 12 months of exposure to BCG.[35] Combination therapy with gemcitabine and docetaxel has been shown to produce a treatment success rate of 32% at 2 years but results are dependent on the type of BCG failure.[36] Emerging therapies include adenovirus IFN-α gene therapy (instilladrin), which shows disease-free survival of 30% at 1 year,[37] adenovirus vector CG0070 for granulocyte-macrophage colony-stimulating factor,[38] FGFR3 inhibitors, mTOR pathway (everolimus plus gemcitabine), and EpCAM (vicinium). Despite these promising therapies, it is important to recognise that radical cystectomy is the treatment of choice in patients who have genuinely failed BCG or are BCG unresponsive, and that it should be instigated before patient disease progresses to T2.[39]

In conclusion, for patients with BCG unresponsive disease who refuse radical cystectomy (which still represents the 'safest' option), personalised therapy with directed use of instillation therapy as a salvage treatment can be offered.

Meeting Close

Professor Per-Uno Malmström

The results of the audience voting at the beginning and at the end of the symposium showed a shift in attitudes toward the use of TURB in blue light and device assisted MMC administration (Figure 1 and Figure 2).

The treatment of NMIBC is an important topic, one that is still in need of optimisation. Treatment should be tailored to the individual patient, and it does not necessarily follow that a patient with a recurrence after BCG treatment needs a cystectomy; if the recurrence is detected 2 years after BCG treatment, a rechallenge might prove effective. While single immediate instillation, chemotherapy, and immunotherapy are good options for controlling the recurrence and progression of these patients, the most important step in the management of NMIBC is an optimal TURB.

REFERENCES

1. Leal J et al. Economic Burden of Bladder Cancer Across the European Union. Eur Urol. 2016;69(3):438-47.

2. Babjuk M et al. 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. BJU Int. 2005;96(6):798-802.

3. Burger M et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol. 2013;64(5):846-54.

4. Babjuk M et al.; European Association of Urology. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013;64(4):639-53.

5. Järvinen R et al. Long-term efficacy of maintenance bacillus Calmette-Guérin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma in situ: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. Eur Urol. 2009;56(2): 260-5.

6. Malmström PU et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56(2):247-56.

7. Borkowska EM et al. Molecular subtyping of bladder cancer using Kohonen self-organizing maps. Cancer Med. 2014;3(5):1225-34.

8. Sylvester RJ et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49(3):466-467.

9. Fernandez-Gomez J et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009; 182(5):2195-203.

10. Kamat AM et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. J Urol. 2014;192(2):305-15.

11. Stenzl A et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol. 2009;55(4):815-25.

12. Sylvester RJ et al. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol. 2004;171(6 Pt 1):2186-90.

13. Uroweb. Non-muscle-invasive Bladder Cancer. Available at: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/. Last accessed: 18 March 2016.

14. Gudjónsson S et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. Eur Urol. 2009;55(4):773-80.

15. Sylvester RJ et al. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection with transurethral resection alone in patients with Stage pTa-pT1 urothelial carcinoma of the bladder: Which patients benefit from the instillation? Eur Urol. 2016;69(2): 231-44.

16. Oddens JR et al. One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? Eur Urol. 2004;46(3):336-8.

17. Bolenz C et al. Intravesical mitomycin C for superficial transitional cell carcinoma. Expert Rev Anticancer Ther. 2006;6(8):1273-82.

18. Comploj E et al. Perforation during TUR of bladder tumours influences the natural history of superficial bladder cancer. World J Urol. 2014;32(5):1219-23.

19. Kausch I et al. Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. Eur Urol. 2010;57(4):595-606.

20. Folkman J et al. Isolation of a tumor factor responsible for angiogenesis. J Exp Med. 1971;133(2):275-88.

21. Lee JY et al. A network meta-analysis of therapeutic outcomes after new image technology-assisted transurethral resection for non-muscle invasive bladder cancer: 5-aminolaevulinic acid fluorescence vs hexylaminolevulinate fluorescence vs narrow band imaging. BMC Cancer. 2015;15:566.

22. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management | Guidance and guidelines. Available at: https://www.nice.org.uk/guidance/ng2. Last accessed: 18 March 2016.

23. Lamm DL et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163(4):1124-9.

24. Kamat AM, Porten S. Myths and mysteries surrounding bacillus Calmette-Guérin therapy for bladder cancer. Eur Urol. 2014;65(2):267-9.

25. Martin FM, Kamat AM. Definition and management of patients with bladder cancer who fail BCG therapy. Expert Rev Anticancer Ther. 2009;9(6):815-20.

26. Kamat AM et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: Recommendations from the International Bladder Cancer Group. J Clin Oncol Off J Am Soc Clin Oncol. 2016. [Epub ahead of print].

27. Catalona WJ et al. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol. 1987;137(2):220-4.

28. Raj GV et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. J Urol. 2007;177(4):1283-6.

29. Gallagher BL et al. Impact of previous bacille Calmette-Guérin failure pattern on subsequent response to bacille Calmette-Guérin plus interferon intravesical therapy. Urology. 2008;71(2):297-301.

30. Hemdan T et al. 5-Year outcome of a randomized prospective study comparing bacillus Calmette-Guérin with epirubicin and interferon-α2b in patients with T1 bladder cancer. J Urol. 2014;191(5):1244-9.

31. Morales A et al. Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guérin. J Urol. 2015;193(4):1135-43.

32. Dinney CPN et al. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. Urol Oncol. 2013;31(8):1635-42.

33. Dalbagni G et al. Phase II trial of intravesical gemcitabine in bacille Calmette-Guérin-refractory transitional cell carcinoma of the bladder. J Clin Oncol Off J Am Soc Clin Oncol. 2006; 24(18):2729-34.

34. Skinner EC et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. J Urol. 2013;190(4):1200-4.

35. Nativ O et al. Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. J Urol. 2009;182(4):1313-7.

36. Steinberg RL et al. Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer. Bladder Cancer. 2015;1(1):65-72.

37. Tao Z et al. Efficacy of a single intravesical treatment with Ad-IFN/Syn 3 is dependent on dose and urine IFN concentration obtained: implications for clinical investigation. Cancer Gene Ther. 2006;13(2):125-30.

38. Burke JM et al. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. J Urol. 2012;188(6):2391-7.

39. Boström PJ et al. Optimal timing of radical cystectomy in T1 high-grade bladder cancer. Expert Rev Anticancer Ther. 2010;10(12):1891-902.

PREVENTION AND MANAGEMENT OF BIOPSY COMPLICATIONS

***Tommaso Cai**

Department of Urology,
Santa Chiara Hospital, Trento, Italy
**Correspondence to ktommy@libero.it*

Prostate biopsy is currently an essential procedure for prostate cancer diagnosis and the transrectal approach is most commonly used by European urologists.[1] Even though transrectal prostate biopsy (TR-PB) is generally considered a safe procedure, it may be accompanied by several clinical complications.[2] In the last few years, we have observed a higher number of infectious complications reported after the procedure compared with other complication types.[1-3] The higher rate of sepsis could be due to the emerging resistance to fluoroquinolones.[3-4] Today, the infective complications after TR-PB represent an important challenge for the urologist and a life-threatening risk for the patient, in particular due to the increased rate of antibiotic-resistant bacteria. We need to focus our attention on the prevention of infective complications and find novel approaches and strategies.

INFECTIVE COMPLICATIONS: THE SIZE OF THE PROBLEM

Even with fluoroquinolones being the most prescribed drug for TR-PB prophylaxis, in line with European Association of Urology (EAU) guidelines,[5] the hospital admission rates due to complications following TR-PB have increased dramatically during the last 10 years.[3,6] The recently published results of the Global Prevalence Study of Infections in Urology study showed a high rate of symptomatic urinary tract infections (5.2%) and a significant rate of hospitalisation (3.1%).[3] In the same study, Wagenlehner et al.[3] reported that fluoroquinolones were administered to 98.2% of patients, in accordance with the EAU guidelines, but the resistance rate against fluoroquinolones was seen in 60% of all isolated bacterial strains. Moreover, several studies showed that the higher risk of infection is due to an increase in ciprofloxacin resistance in *Escherichia coli* and hence a concomitant decrease in the efficacy of ciprofloxacin prophylaxis in patients undergoing TR-PB.[7] The recent increase of fluoroquinolone-resistant organisms has become a true contemporary health emergency (Figure 1). This condition is due both to the misuse and over-prescription of antibiotics and the limited research on new molecules, meaning that there is a reduced number of new antibiotics planned by pharmaceutical companies.[6]

INFECTIVE COMPLICATIONS: ALTERNATIVE STRATEGIES TO DECREASE INFECTIVE COMPLICATIONS

Several strategies have been proposed and evaluated to prevent infective complications after TR-PB:

1. Risk assessment to select patients at higher risk for infective complications:
- Identify patients at higher risk of infective complications
2. Microbiological sampling of the faecal flora prior to biopsy to identify resistance to specific agents:
- Consider that rectal swab would represent a substantial burden for clinical microbiology laboratories and might fail to detect ciprofloxacin-sensitive isolates with borderline minimum inhibitory concentrations
3. Biopsy cores and the use of targeted, image fusion guided biopsies and change of biopsy route (perineal approach):
- Even if TR-PB is convenient, cheap, and quick to perform, please consider the transperineal approach as an option to all patients in whom a high risk of infective complication has been found
4. Alternative antibiotics with improved susceptibility to be used for prophylaxis:
- The rising resistance to fluoroquinolones such as ciprofloxacin is the most likely cause of the increasing prevalence of infectious

complications after TR-PB, and novel approaches for antibacterial prophylaxis need to be designed and evaluated accordingly. Fosfomycin seems a candidate alternative agent for antibiotic prophylaxis in TR-PB, having shown elevated activity against multidrug-resistant Gram-negative bacteria and favourable pharmacokinetic parameters, including an elevated penetration into prostatic tissue[8-9]

TAKE HOME MESSAGES

In conclusion, from all the evidence it is clear that prostate biopsy policy should be totally revised in order to obtain acceptable prospective results in terms of infective complications, cost saving, and patient compliance. In everyday clinical practice, please take into account the following aspects:

- A detailed evaluation of all risk factors for infectious complications (i.e. diabetes and previous use of antibiotics for urinary tract infections)
- Evaluation of all risk factors for harbouring resistant organisms (i.e. recent hospitalisation, travel to certain geographical regions, or antibiotic use)
- The role of alternative strategies for reducing the risk of infective complications

REFERENCES

1. Chun FK et al. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. Eur Urol. 2010;58(6):851-64.

2. Cai T et al. Infectious complications after prostate biopsy: Time to rethink our clinical practice. World J Clin Urol. 2015;4(2):83-91.

3. Wagenlehner FM et al.; GPIU investigators. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol. 2013;63(3):521-7.

4. Loeb S et al. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol. 2012;61(6):1110-4.

5. European Association of Urology. Guidelines on Urological Infections. 2014. Available at: http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf. Last accessed: 18 March 2016.

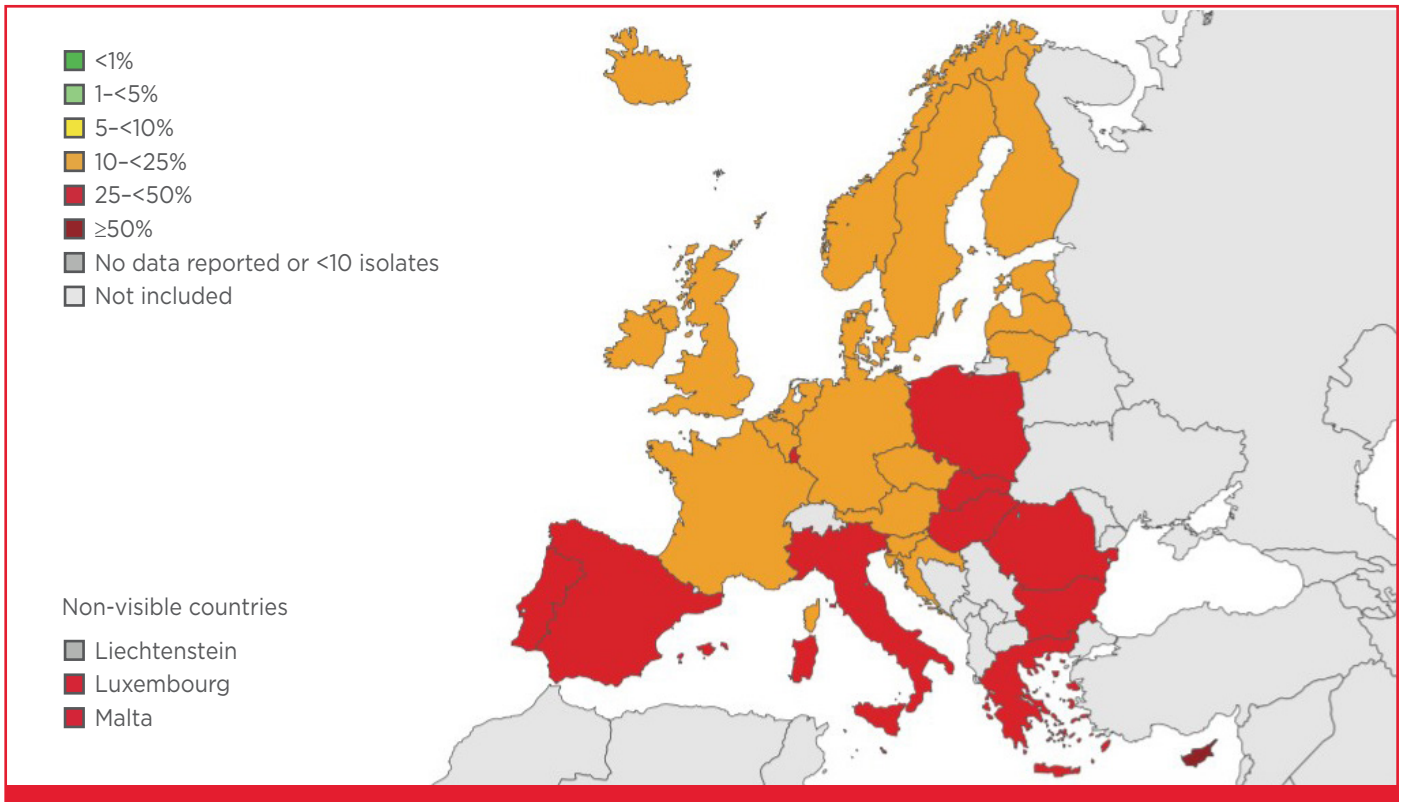


Figure 1: Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2013. Antimicrobial resistance surveillance in Europe, 2013. Annual report of the European Antimicrobial Resistance Surveillance Network.[10]

6. Bartoletti R, Cai T. Prostate biopsies should be performed according to a standard of care. Eur Urol. 2013;63(6):528-9.

7. Carignan A et al. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: time to reassess antimicrobial prophylaxis? Eur Urol. 2012;62(3):453-9.

8. Falagas ME et al. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis. 2010;10(1):43-50.

9. Lista F et al. Efficacy and safety of fosfomycin-trometamol in the prophylaxis for transrectal prostate biopsy. Prospective randomized comparison with ciprofloxacin. Actas Urol Esp. 2014;38(6):391-6.

10. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2013. Annual Report of the European Antimicrobial Surveillance Network (EARS-Net). 2014. Available at: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2013.pdf. Last accessed: 18 March 2016.

HIGH POWER (200W) THULIUM LASER VAPORISATION OF THE PROSTATE WITH THE OYSTER TECHNIQUE: INITIAL EXPERIENCE AND EARLY POSTOPERATIVE OUTCOMES

***Panagiotis Kallidonis, Iason Kyriazis, Wissam Kamal, Evangelos Liatsikos**

Department of Urology, University of Patras, Patras, Greece
**Correspondence to pkallidonis@yahoo.com*

Laser treatment of bladder outlet obstruction related to benign hyperplasia has gained wide acceptance during the last decade. The thulium:yttrium aluminium garnet laser (Tm:YAG) has been successfully used for treatment of the above condition with several studies demonstrating its safety and efficacy.[1,2] Since the introduction of the thulium laser, the available energy in thulium laser systems has been raised from 70W to 120W and finally to 150W.

Recently, a 200W high power Tm:YAG laser, the Revolix 200 (Lisa laser products OHG, Katlenburg-Lindau, Germany) became available. This study aimed to evaluate the safety and feasibility of 200W high power Tm:YAG laser prostatectomy and to present the early postoperative outcomes of the approach. In addition, a specific technique based on the combination of enucleation of the middle lobe and vaporesection of the adenoma was performed. In short, the middle lobe of the prostate is enucleated without being completely released to the bladder. The middle lobe and the lateral lobes are then vaporised and resected simultaneously.[3]

Nineteen patients underwent the aforementioned technique. Patients with a prostate volume >40 mL and a lack of detrusor underactivity on preoperative urodynamic evaluation were included. A follow-up evaluation at 3 months was available for all patients. The mean laser time duration was 32.5 minutes, serum sodium levels were not significantly reduced, and the mean haemoglobin drop was 0.71 g/dL (range 0–1.7). Transfusion was deemed necessary in one case and another patient developed transient fever. The majority of the patients were catheter free (n=14) on postoperative Day 1. A catheter was re-inserted in one patient. Re-interventions were not necessary in the 3 months of follow-up. Mean hospitalisation time was 1.95 days. During the follow-up period reduction of the mean International Prostate Symptom Score was seen in 62.8% of the patients and improvement of mean maximum urinary flow rate was noted in 58%. All but one patient reported favourable changes in their quality of life. Mild dysuria was present in 58% of patients. No cases of postoperative incontinence, urethral strictures, or significant post-voided residual urine volume were documented.

Despite the lack of a comparative group, the above results were promising and comparable to the literature.[1,2] The safety of the technique was clear. Significant complications or re-interventions did

not occur. The recorded operative times suggest a high efficiency of the 200W vaporesection. Any advantages or disadvantages of the 200W Tm:YAG vaporesection would be elucidated with appropriate comparative studies. It should be noted that a randomised trial comparing the Tm:YAG laser prostatectomy to the transurethral resection of the prostate is ongoing at our institution. The current results represent a preliminary study and represent the learning curve of the surgeon who is performing the treatments in the aforementioned trial. Thus, improved surgical and clinical outcome could be expected.

REFERENCES

1. Karl A, Herrmann TR. En bloc resection of urothelial cancer within the urinary bladder: the upcoming gold standard? : Re: Kramer MW, Wolters M, Cash H, Jutzi S, Imkamp F, Kuczyk MA, Merseburger AS, Herrmann TR. Current evidence of transurethral Ho:YAG and Tm:YAG treatment of bladder cancer: update 2014. World J Urol. 2014 Jun 10. [Epub ahead of print]. doi: 10.1007/s00345-014-1337-y. World J Urol. 2015;33(4):581-2.

2. Zhu Y et al. Thulium laser versus standard transurethral resection of the prostate for benign prostatic obstruction: a systematic review and meta-analysis. World J Urol. 2015;33(4):509-15.

3. Chung JS et al. Thulium laser (RevoLix) vaporesection versus vapoenucleation with morcellator (Piranha) for the treatment of benign prostatic obstruction: a propensity-matched multicenter analysis. Int J Urol. 2014;21(11):1156-61.

ROBOTIC LAPAROENDOSCOPIC SINGLE-SITE RADICAL PROSTATECTOMY: IDEAL PHASE I

***Franco Gaboardi, Giovannalberto Pini**

Department of Urology Turro Section, San Raffaele Hospital Milano, Milan, Italy
**Correspondence to gaboardi.franco@hsr.it*

Laparoendoscopic single-site surgery (LESS) represents any minimally invasive intra-abdominal surgical procedure performed through a single incision/location and aims to reduce the already limited invasiveness of conventional laparoscopy even further, to offer not only a better cosmetic result, but also to potentially reduce post-operative pain and offer a quicker convalescence.[1]

After >900 laparoscopic radical prostatectomies (RPs) performed since 2001,[2,3] in 2009 we accomplished our first LESS RP. It cannot be denied that some limitations were encountered. Placing several parallel instruments in a single multichannel port made triangulation more difficult, reducing proper tissue retraction and resulting in clashing of the laparoscope with instruments and a limited operating field. These difficulties were particularly disturbing during the reconstruction phase, when performing vesicourethral anastomosis. Some authors suggested the use of bent, articulated, and different length instruments (i.e. obese and paediatric equipment).[4,5] We have personally always adopted an extra 5 mm port placed in the left fossa iliaca.[6] As a matter of fact, a recent multi-institutional study[7] confirmed that the use of an additional port occurred in 23% of the cases.

In order to overcome these limitations, we presented our preliminary experience (IDEAL Phase I)[8] with robotic-LESS RP performed with the da Vinci® single-site robotic platform (Intuitive Surgical, Sunnyvale, California, USA), a semirigid operative system with that incorporates a multichannel single port that accommodates two curved robotic cannulas. The master-slave software automatically exchanges the master-slave controls allowing the surgeon at the console to control the tip of the instrument with their right hand at the right side of the surgical field and the opposite for the left.

At this stage, not all surgical instruments have the wrist at the tip like conventional robotic da Vinci instruments (Intuitive Surgical, Sunnyvale, California, USA) do. We suggest a handmade port-access by combining the single-site multichannel Alexis® wound retractor, and the laparoscopic cap (Applied Medical, California, USA) (Figure 1). The robotic instruments adopted were two endo-wrist needle drivers and a hook, along with the Filbloc® barbed suture (Assut, Rome, Italy) (Figure 2).

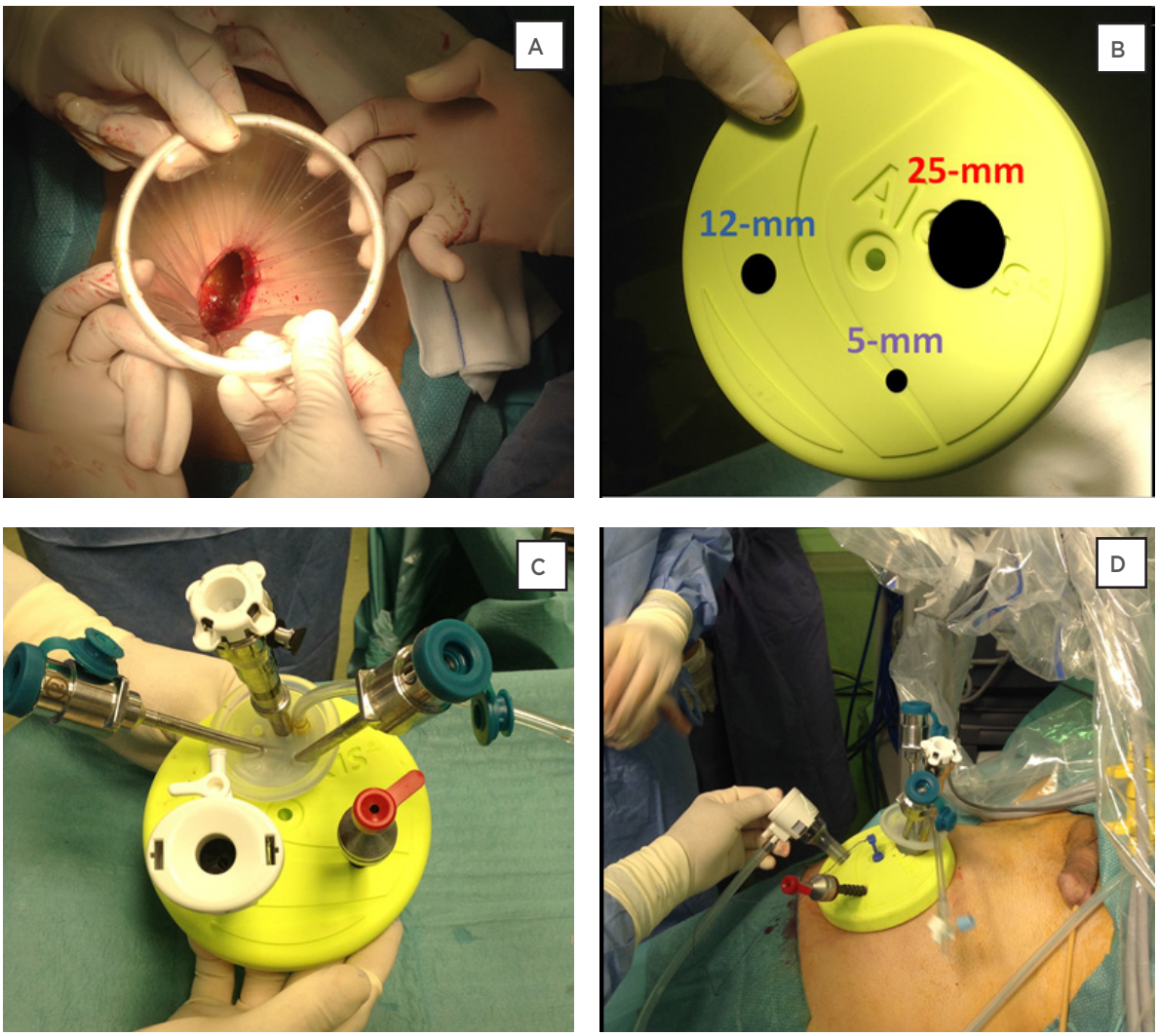


Figure 1: Handmade port-access.
A) We performed a 5 cm paraumbilical incision and introduced the Alexis wound retractor. B,C) We inserted, through 3 entry-holes made in the laparoscopic cap (25 mm, 12 mm, and 5 mm), the multichannel port and a 12 mm and a 5 mm trocar. D) Finally we plugged the handmade ports and docked the robot.

Operative time for the very first procedure was 310 minutes and dropped to 210 minutes by the third case. The assistant was able to simultaneously use two different laparoscopic instruments and easily apply 10 mm clips. A robotic needle-driver was used as a grasper in order to confer more traction and firmness to tissue. There was no need to convert to hybrid robotic-LESS (2 ports) or a standard robotic-approach (5–6 ports) in the three surgeries performed. Mean blood loss was 150 mL and there were no intraoperative or postoperative complications. Patients were discharged on the 3rd postoperative day and their catheters were removed on the 7th postoperative day following urethrocystogram.

This Phase I IDEAL study demonstrated that a pure Robotic-LESS-RP performed with the new dedicated platform in combination with a handmade port is feasible and safe, eliminates instrument crossing, and offers superior ergonomics for both the robotic surgeon and the bedside assistant, whilst the needle-driver tip articulation significantly facilitates suturing.

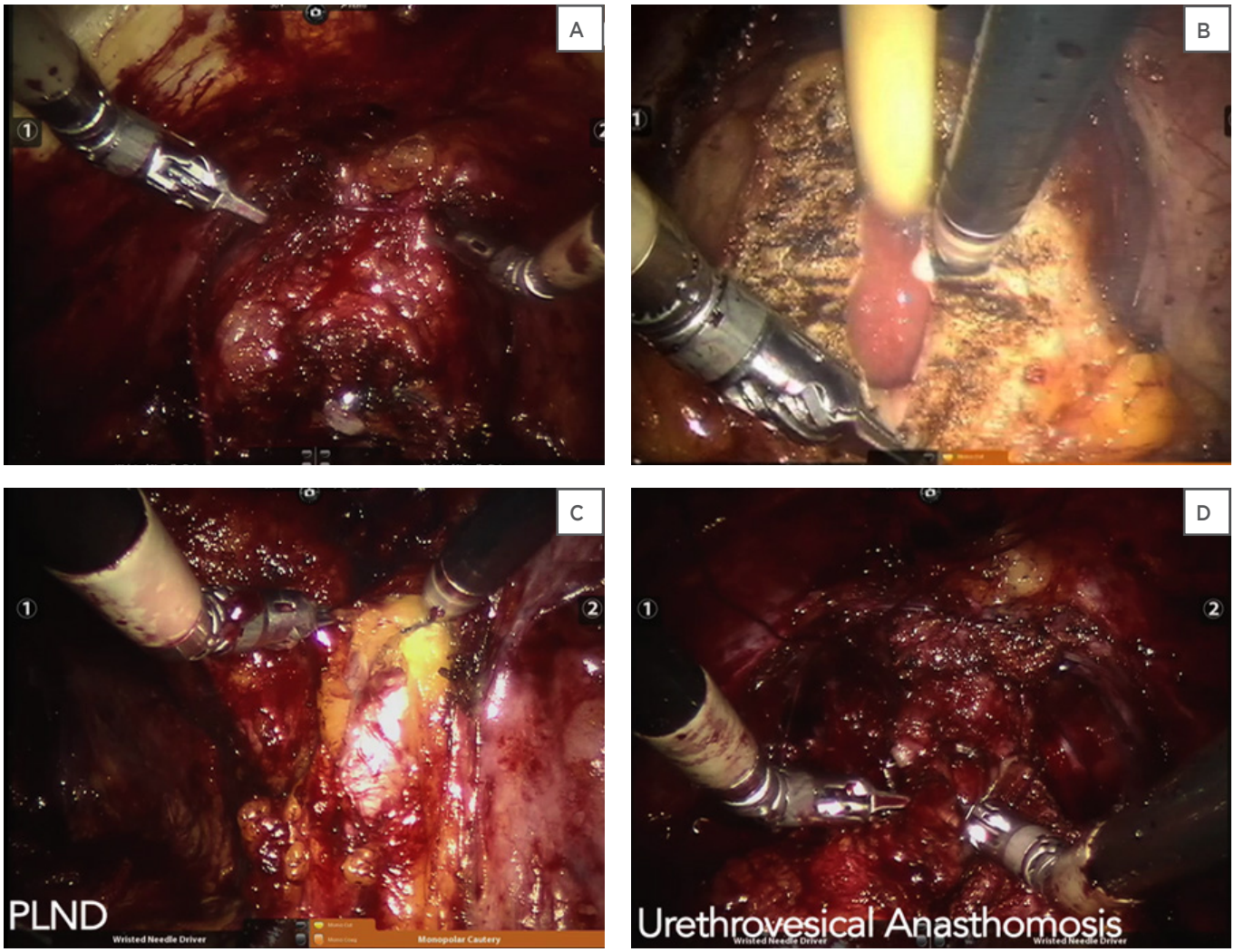


Figure 2: Surgical Steps.
A) Dorsal venous complex (Santorini's plexus) suture, B) bladder-neck dissection, C) extended pelvic lymph node dissection (PLND), D) urethrovesical anastomosis.

The lack of endo-wrist technology applied to other instruments (scissors and forceps) requires improvement.

REFERENCES

1. Box G et al. Nomenclature of natural orifice translumenal endoscopic surgery (NOTES) and laparoendoscopic single-site surgery (LESS) procedures in urology. J Endourol. 2008;22(11):2575-81.

2. Gregori A et al. Laparoscopic radical prostatectomy: perioperative complications in an initial and consecutive series of 80 cases. Eur Urol. 2003;44(2):190-4.

3. Galli S et al. Oncologic outcome and continence recovery after laparoscopic radical prostatectomy: 3 years' follow-up in a "second generation center". Eur Urol. 2006;49(5):859-65.

4. Pini G et al. Costs analysis of laparoendoscopic, single-site laparoscopic and open surgery for cT1 renal masses in a European high-volume center. World J Urol. 2014;32(6):1501-10.

5. Pini G, Rassweiler J. Minilaparoscopy and laparoendoscopic single-site surgery: mini- and single-scar in urology. Minim Invasive Ther Allied Technol. 2012;21(1):8-25.

6. Gaboardi F et al. 'LESS' radical prostatectomy: a pilot feasibility study with a personal original technique. BJU Int. 2011;107(3):460-4.

7. Kaouk JH et al. Laparoendoscopic single-site surgery in urology: worldwide multi-institutional analysis of 1076 cases. Eur Urol. 2001;60(5):998-1005.

8. McCulloch P et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.

ENURESIS AND URINARY INFECTIONS IN CHILDHOOD: BAD NEWS FOR YOUNG WOMEN?

***Ester Illiano,[1] Kostantinos Giannitsas,[2] Elisabetta Costantini[1]**

1. Urology and Andrology Clinic, Department of Surgical and Biomedical Science, University of Perugia, Perugia, Italy
2. Department of Urology, University Hospital of Patras, Rio, Greece
**Correspondence to ester.illiano@inwind.it*

One of the most interesting areas of research in urology is the correlation between childhood and adulthood urological conditions. The aim of our multicentre prospective study (registered on ClinicalTrials.gov [NCT02185287] and presented as an abstract at the EAU Annual Congress 2016) was to evaluate if urinary incontinence (UI) and recurrent urinary tract infections (rUTIs) in women 18–40 years old are the result of previous paediatric urological diseases. These results may identify the 'risk conditions', which, if treated properly in early childhood, could help avoid debilitating diseases that manifest themselves in adults and possibly help us design and implement a prevention strategy. We enrolled 254 women (age 18–40 years) divided into two groups: healthy volunteers (n=134) and patients (n=120) with any urinary symptoms, presenting at nine Italian urological clinics. We asked all the patients to complete a 77-item questionnaire, which consisted of two parts: part one explores the females' urological and bowel history until the age of 14 years, part two refers to the current (adulthood) urological, bowel, and sexual history. The first part was completed with the help of parents or relatives, if required. There was a higher percentage of childhood nocturnal enuresis (NE) and rUTI in the patient group compared with the volunteer group. (7% versus 6%, and 18% versus 6%, respectively). These results are in line with data in the literature, where the prevalence of NE is 8%[1] and the prevalence of rUTIs 20–48%.[2] Women with NE during childhood had a higher prevalence of UI during adulthood compared with girls without NE (55% versus 45%, p=0.002). The relationship between childhood NE and UI has been investigated in a couple of studies. For example, Yarnell et al.[3] showed an increased relative risk of having UI in women with a history of NE after the age of 9 years, Foldspang et al.[4] reported an association between childhood NE and urgency UI, and Ayse et al.[5] showed a correlation between stress UI and NE. The increased risk of adulthood UI in women with a history of childhood NE may be explained by the presence of a congenital dysfunction or impairment in afferent and/or efferent bladder innervation, which initially leads to NE and later presents as UI. Recurrent UTIs remain an important public health problem in women of all ages. Our study, in accordance with research by Raz et al.,[6] showed that women with rUTI during childhood had higher prevalence of rUTI during adulthood compared with women without history of rUTI (p=0.02). A probable explanation of this correlation is a genetic predisposition or a long-term histopathological alteration of the urothelium. There was also a correlation between childhood constipation and rUTI in adulthood, linking gastrointestinal problems as a possible risk factor for later UTIs.

In conclusion, our data demonstrated that there is an important correlation between childhood and adulthood urological conditions. Girls with NE or rUTIs should be carefully monitored to ensure adequate treatment of these conditions, or should follow a prevention strategy to avoid adulthood symptoms. To achieve this, a close collaboration between paediatricians and urologists is mandatory.

REFERENCES

1. Kawauchi A et al. Follow-up study of bedwetting from 3 to 5 years of age. Urology. 2001;58(5):772-6.

2. Williams GJ et al. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev. 2006;3:CD001534.

3. Yarnell JW et al. Factors associated with urinary incontinence in women. J Epidemiol Community Health. 1982;36(1):58-63.

4. Foldspang A et al. Adult female urinary incontinence and

childhood bedwetting. J Urol. 1994;152(1):85-8.

5. Ayse G et al. Enuresis in childhood, and urinary and fecal incontinence in adult life: do they share a common cause? BJU Int. 2005;95:1058-62.

6. Raz R et al. Recurrent urinary tract infections in postmenopausal women. Clin Infect Dis. 2000;30(1):152-6.

ADJUVANT VERSUS EARLY SALVAGE RADIATION THERAPY AFTER RADICAL PROSTATECTOMY: A TRULY FAIR COMPARISON?

***R. Jeffrey Karnes, Alessandro Morlacco**

Department of Urology, Mayo Clinic, Rochester, Minnesota, USA
**Correspondence to karnes.r@mayo.edu*

Objective: To discuss the current evidence supporting the use of adjuvant radiation therapy (ART) versus early salvage radiation therapy (eSRT) in the post-prostatectomy setting, and the available tools for patient selection.

Research process/evidence synthesis: Post-surgery radiation therapy (RT) is commonly used as a secondary therapy to maximise local control and long-term oncological outcomes in patients who present with adverse features at radical prostatectomy (RP). According to most guidelines, the presence of seminal vesicle invasion, positive surgical margins, extraprostatic extension, and/or positive lymph nodes may indicate a beneficial use of post-surgical RT.[1,2] ART is the administration of RT with an undetectable postoperative prostate-specific antigen (PSA), while eSRT is prescribed to patients with biochemical recurrence (BCR), low PSA levels (<0.5 ng/mL), and no evidence of systemic spread. The three main randomised clinical trials dealing with ART versus initial observation have shown a benefit in reducing BCR; only one trial (SWOG 8794) suggested a benefit in metastasis-free and overall survival,[3–5] though it received sharp criticism.[6] Unfortunately, these trials share some critical limitations: two of them did not require an undetectable PSA for inclusion, the approach at BCR was unstandardised (only a fraction of patients received salvage radiation therapy [SRT]), and many patients who underwent SRT did so at an advanced stage (clinically detectable or even symptomatic local recurrence).

ART carries a risk of overtreatment as a substantial proportion of men with few adverse pathological characteristics will not recur after surgery,[3–5,7] and uniform RT represents a source of potential morbidity.[8]

Administering immediate RT to the patients at highest risk of early progression without compromising the opportunity of cancer control in men with BCR is a challenge within modern urological oncology. The three randomised clinical trials say little about the role of eSRT in comparison to immediate ART.

In recent years, many centres have gathered retrospective evidence supporting SRT. Positive results (5-year BCR-free survival of 71%) were shown by a 2014 systematic review by Pfister et al.,[9] which included 10 retrospective studies, though most of these studies did not have the power to make any comparison between ART and eSRT. However, one study by Briganti et al.[10] used a propensity-score matched analysis in a population of T3pN0 R0/1 patients who underwent ART or observation with eSRT, and did not find differences in 2 and 5-year BCR free survival. Abdollah et al.[7] confirmed that not all patients with adverse pathological features achieve the same benefit from ART; only two or more risk factors (pGS 8, stage pT3b/4, and positive lymph node count >1) were associated with significant ART benefit on survival in their study, while monitoring with or without eSRT might be an option for the others. Nonetheless, there is a clear need for higher quality evidence. Currently, at least three ongoing randomised clinical trials (RADICALS RT, GETUG 17, and RAVES) are expected to provide valuable answers, but mature survival results will not be available for several years.

Multivariate models and nomograms (CAPRA-S score,[11] Stephenson,[12] and Abdollah[7] nomograms) have shown good accuracy and may be used to predict post-RP mortality and inform risk-adapted decisions for ART or initial monitoring. However, deeper knowledge of prostate cancer intimate biology is expected to provide more precise tools. As an example, a genomic classifier has outperformed CAPRA-S in post-RP outcome prediction and demonstrated accuracy in identifying patients who may benefit more from ART versus those amenable to observation with or without SRT.[13]

Conclusion: The optimal timing of post-operative RP is still an unresolved issue for many. Until higher level evidence is available, initial observation may be a viable option in an effort to balance cost, toxicity, and oncological control. Risk-adapted approaches, using clinical and biological information, are becoming more and more promising.

REFERENCES

1. Mottet N et al. EAU 2015. Guidelines on Prostate Cancer. Available at: http://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf. Last accessed: 10 March 2016.

2. National Comprehensive Cancer Network. NCCN Guidelines for Patients: Prostate Cancer Version 1. 2016. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Last accessed: 10 March 2016.

3. Bolla M et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 380(9858):2018-27.

4. Thompson IM Jr et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA. 2006;296(19):2329-35.

5. Wiegel T et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol. 2009;27(18):2924-30.

6. D'Amico AV. Adjuvant versus salvage post-prostatectomy radiation therapy: a critical review of the evidence. J Urol. 2013;190(2):450-1.

7. Abdollah F et al. Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer : a long-term survival analysis. Eur Urol. 2013;63(6):998-1008.

8. Suardi N et al. Impact of adjuvant radiation therapy on urinary continence recovery after radical prostatectomy. Eur Urol. 65(3);546-51.

9. Pfister D et al. Early salvage radiotherapy following radical prostatectomy. Eur Urol. 2014;65(6):1034-43.

10. Briganti A et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. Eur Urol. 2012;62(3):472-87.

11. Cooperberg MR et al. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer. 2011;117(22):5039-46.

12. Stephenson AJ et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol. 2005;23(28):7005-12.

13. Den RB et al. Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy. J Clin Oncol. 2015;33(8):944-51.

INFLUENCE OF SOCIAL MEDIA ON UROLOGICAL KNOWLEDGE ACQUISITION AMONG YOUNG UROLOGISTS ACROSS EUROPE

***Juan Gomez Rivas,[1] Pieter Uvin,[2] Moises Rodriguez Socarras,[3] Giulio Patruno,[4] Francesco Esperto,[5] Paulo Jorge Dinis,[6] Hendrik Borgmann[7]**

1. Department of Urology, La Paz University Hospital, Madrid, Spain
2. University Hospitals Leuven, Leuven, Belgium
3. Department of Urology, University Hospital Álvaro Cunqueiro, Vigo, Spain
4. University of Rome Tor Vergata, Rome, Italy
5. Sapienza Università di Roma, Rome, Italy
6. Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
7. Department of Urology, University Hospital Frankfurt, Frankfurt, Germany
**Correspondence to juangomezr@gmail.com*

Communication is part of human nature and the need for faster communication has resulted in the development of different methods such as

mailing, printing, phones, mobiles, computers, and the internet, which have all changed the course of human history. Advances in communication have always allowed the evolution of cultures. Nowadays, Social Media (SoMe) is changing the way people live, communicate, and interact globally. The applications of SoMe in healthcare and its role in scientific communication represents a growing area of interest that is providing great opportunities in the urological community. In our study we aimed to assess the influence of SoMe on urological knowledge acquisition among young urologists across Europe.

The European Society of Residents in Urology, German Society of Residents in Urology, and the Spanish Residents and Young Urologists Workgroup members designed a 20-item online survey. The survey was distributed via email in 23 European countries to urology residents and young urologists. Survey design and distribution was performed in concordance with the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines. SPSS (IBM, New York, USA) was used for statistical calculations comparing the use of SoMe in urologists in two age groups with a cut-off of 35 years of age.

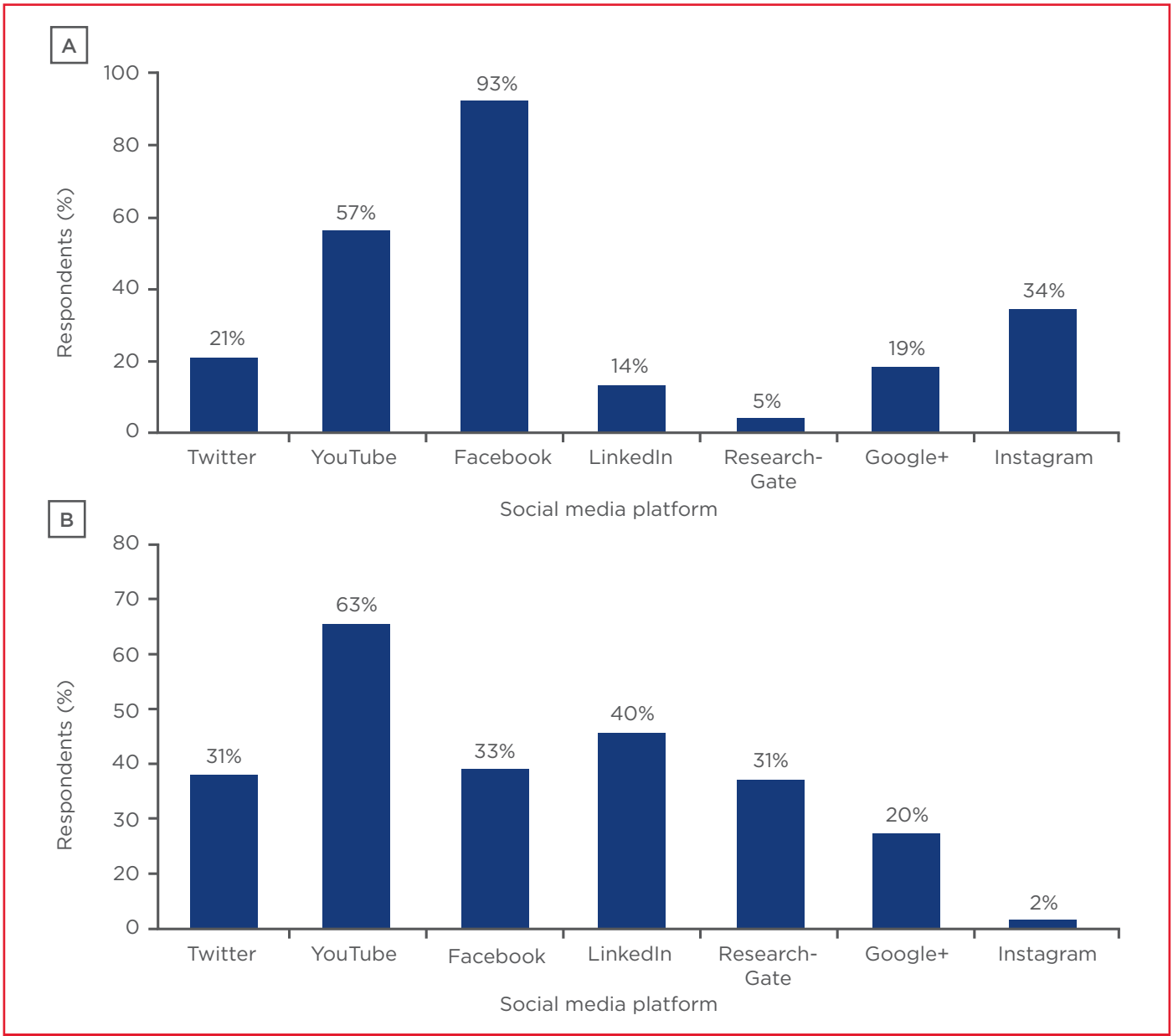


Figure 1: Usage rates of social media platforms for personal A) and professional B) purposes.

Three hundred and sixteen residents and young urologists with a mean age of 31.2±3.9 years responded to the survey; of these residents, 79% were in training with a mean of 4.1±3.0 years of training, and 21% were certified urologists. SoMe was used by 99% of respondents in personal and professional capacities. Facebook was the most frequently used platform for personal use whilst YouTube and LinkedIn were used most frequently for professional use (Figure 1). A total of 44% of the respondents had an academic or professional profile on a SoMe platform. SoMe was ranked in third place as an information source for urological news and updates behind journals and websites, and ahead of congresses and books. Video content from YouTube or other sources was ranked as the preferred tool to see/understand surgical techniques ahead of websites and reference books. Sixty-one percent of respondents followed urological associations, 47% followed urological events, 44% followed urological journals, and 39% followed urological experts on SoMe. The influence of SoMe on urology knowledge was rated as moderate-to-high by 63% of young urologists and as low-to-none by 37%. The application of guidelines on the appropriate use of SoMe in urology was observed in 44%. Comparative analysis of respondents' SoMe use revealed that certified urologists rated the influence of SoMe on their urology knowledge as higher (p=0.036) and applied SoMe guidelines more frequently (p=0.008) than urology residents.

With these findings we may conclude that SoMe plays a significant role in the knowledge acquisition of young urologists in Europe. SoMe represents a vibrant arena of opportunities for the communication of knowledge in healthcare, and their potential application today is unquestionable. At present the benefits include communication between associations, urologists, residents, other healthcare professionals, and patients. SoMe facilitates networking and dissemination of studies' results, as well as extensive experience of events, conferences, and meetings. Physicians, organisations, and institutions should strive to spread and provide valuable educational content through SoMe.

A NEW MODEL TO PREDICT RISK OF RECURRENCE DURING FOLLOW-UP AFTER RADICAL PROSTATECTOMY

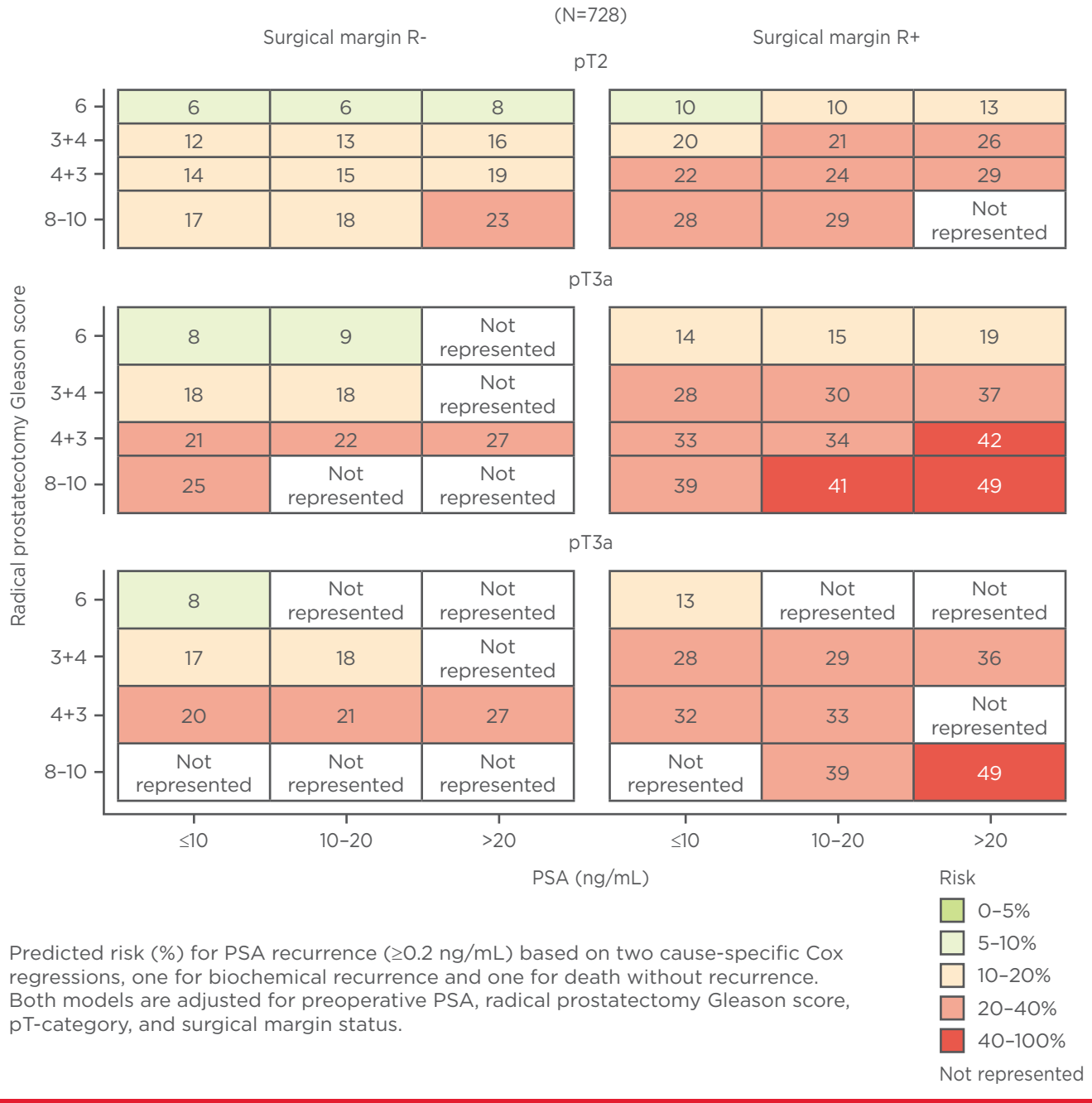
***Martin Andreas Røder,[1] Kasper Drimer Berg,[1] Frederik Birkebæk Thomsen,[1] Sorel Kurbegovic,[1] Helene Charlotte Rytgaard,[2] Lisa Gruschy,[1] Klaus Brasso,[1] Thomas Alexander Gerds,[2] Peter Iversen[1]**

1. Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

2. Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark

**Correspondence to andreasroder@gmail.com*

It is unclear how long patients should be followed after radical prostatectomy (RP) for localised prostate cancer. The evidence is scarce, which relates to the fact that no studies have defined the risk of recurrence at an individual level. The risk of recurrence after RP is highly dependent on prostate specific antigen (PSA) level and tumour characteristics prior to and after surgery. Moreover, the risk is dependent on the length of follow-up, i.e. the risk declines the longer patients remain without recurrence. Also, in a population of patients who have undergone RP the risk of recurrence is affected by other events that may happen before, most importantly death due to other causes without recurrence. This must be accounted for when trying to describe the risk of recurrence in men undergoing surgery for prostate cancer.



Predicted risk (%) for PSA recurrence (≥0.2 ng/mL) based on two cause-specific Cox regressions, one for biochemical recurrence and one for death without recurrence. Both models are adjusted for preoperative PSA, radical prostatectomy Gleason score, pT-category, and surgical margin status.

Figure 1: Risk of prostate specific antigen recurrence in the next 5 years after 5 years of follow-up.
The patients presented here are alive and without recurrence. 'Not represented' means that the specific patient group has either experienced recurrence or is no longer alive.
PSA: prostate specific antigen; pT: primary tumour; R: surgical margin status.

We aimed to answer the question: 'If a patient has been followed for X number of years after RP, remained alive and without recurrence, then what is the risk of recurrence in the future?'. To answer this, we developed a new and easily interpretable model to evaluate the risk of PSA recurrence after RP. The model was based on 1,970 consecutive patients who underwent RP from 1995–2013 with complete follow-up. PSA was measured six times within the first 2 years, then once annually. PSA recurrence was defined as the time from surgery to the first PSA reaching ≥0.2 ng/mL. The individualised risk

of biochemical recurrence (BCR) was computed using multiple cause-specific Cox regression including preoperative PSA, primary Tumour (pT) category, RP Gleason score (GS), and surgical margin (R) status. Death without BCR was considered a competing event. The risks of BCR were dynamically updated by moving the time point of prediction in yearly intervals after RP. The risks of BCR within 1 year and within 5 years after the respective time point of prediction are reported. The median follow-up was 4.9 years. The individual risks of BCR were modified in the presence of risk factors. As an example, a patient with pT2, R negative status, GS 7 (3+4) on prostatectomy, a preoperative PSA ≤10 ng/mL, and 5 years of follow-up without BCR, had a predicted risk of BCR of 12% during the next 5 years (Figure 1). External calibration of the model is the primary limitation. The proposed estimates of the individualised risks of BCR during follow-up after RP appear as a new and useful tool when physicians and patients plan follow-up and PSA testing regimens after RP. The model is available as a free iOS-app, searchable under the term 'CPC risk'.

LAPAROSCOPIC COLPOSACROPEXY: CONTINENCE AND SEXUAL OUTCOMES

***Consuelo M. Conde Redondo, Fatima Castroviejo Royo, Luis Antonio Rodriguez Toves, Alejandro García Viña, Jose H. Amon Sesmero, José María Martínez Sagarra**

Hospital Rio Hortega Valladolid, Valladolid, Spain
**Correspondence to ccondere@hotmail.com*

Introduction

Abdominal sacrocolpopexy is associated with a lower rate of recurrent vault prolapse, a reduced grade of residual prolapse, a longer time-to-recurrence, and less dyspareunia compared with the vaginal procedures such as sacrospinous ligament fixation and uterosacral ligament suspension. A recent Cochrane review stated that abdominal sacrocolpopexy is the more effective procedure and is considered by many authors to be the gold standard in the treatment of vaginal vault prolapse. Our objective is to evaluate the efficacy of laparoscopic sacrocervicopexy for apical support in sexually active patients with pelvicorgan prolapse.

Methods

Fifty women with symptomatic prolapse of the central compartment (Pelvic Organ Prolapse Quantitative [POP-Q] Stage 2) underwent laparoscopic sacrocervicopexy. We used Gynemesh PS™ Mesh, which is constructed of knitted filaments of polypropylene. It is a non-absorbable mesh, with excellent strength, durability, and porosity for necessary tissue in growth.

The operating physicians used the synthetic mesh to attach the anterior vaginal wall, posterior vaginal wall, elevator muscles in both sides, and uterosacral ligaments to the sacral promontory without hysterectomy. No anti-incontinence surgery was performed at the same time, even if the patient was incontinent. The patients returned for follow-up examinations 1 month after surgery and then over subsequent years. On follow-up a physician evaluated each patient for the recurrence of genital prolapse and the recurrence of *de novo* development of urinary or bowel symptoms. We define 'surgical failure' as any grade of recurrent prolapse of Stage II or more on the POP-Q test.

Patients also gave feedback about their satisfaction with the procedure using an analogue visual scale, graded from 0–10. Sexual activity was evaluated with the Index of Female Sexual Function (IFSF) questionnaire, which studies six items: desire, arousal, lubrication, orgasm, satisfaction, and pain (Table 1). Incontinence was also evaluated with the International Consultation on Incontinence

Questionnaire (ICIQ-SF). This includes the following sections: S3: How often do you leak urine?; S4: Would you like to know how much urine you leak?; and S5: Overall how much does urine leakage interfere with your everyday life? (Table 2).

Results

- The mean follow-up period was 33 months and the success rate was 90%
- The present study showed an 8.5/10 satisfaction rate
- A high amelioration on incontinence satisfaction, ICIQ-SF 8 versus 2.4 (range 0–21) was displayed. Twenty-two percent were incontinent before surgery
- Only 45% of patients required further incontinence surgery with a Miniarc®. Total incontinence surgery was 10%. The incontinence cure rate was 77.7%, incontinence maintenance was 11.1%, and *de novo* stress urinary incontinence was 2.86%
- Sexual results showed no changes (IFSF 22.75 versus 22.79, no SD)
- No changes in dyspareunia were shown
- Complications: 50% had bowel dysfunction, 5.7% mesh erosion, 2.8% bowel injury during the surgery, and 2.8% iliac injury.
- POP-Q results:
  - Aa -1±1.8 versus -2±0.4
  - Ba +1±2.3 versus -2±1.5
  - C -1±3.4 versus -6±1.2
  - Ap -2±1.3 versus -3±0.6
  - Bp -2±3.1 versus -3±3.2
  - Cystocele recurrence 6.8%

Conclusion

- Laparoscopic sacrocervicopexy is an effective option for sexually active women with pelvic organ prolapse
- No other incontinence surgery should be undertaken at the same time due to the risk of overtreatment

Table 1: Subjective results.

Female Sexual Function Index (FSFI)	PRE	POST
Desire	2.4	2.9
Arousal	3	3.14
Lubrication	3.6	3.8
Orgasm	4	3.45
Satisfaction	4.5	3.6
Pain	3.2	3.6
TOTAL FSFI ICIQ-SF Analogue Visual Scale	20.2 7.17 3	23.8 3.9 8.5

ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form.

Table 2: International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) questionnaire results.

ICIQ-SF	PRE	POST
SF3	1.75	0.95
SF4	1.9	1
SF5	3.39	1.5
Total	7.17	3.9

MID-TERM OUTCOMES FOLLOWING SUBURETHRAL SYNTHETIC SLING REMOVAL IN WOMEN

Himanshu Aggarwal, *Philippe E. Zimmern

Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA
**Correspondence to philippe.zimmern@utsouthwestern.edu*

Although placement of a synthetic midurethral sling (MUS) is the most commonly performed procedure for female stress urinary incontinence (SUI),[1,2] it remains a sling procedure and, as such, can be fraught with secondary complications including voiding dysfunction,[3-5] incontinence,[3-5] pain (8–16%),[6] dyspareunia (6–7.5%),[3,4] and/or vaginal mesh exposure.[3-5]

As a tertiary care centre, we encounter MUS complications at a very high rate, and therefore have to perform several synthetic sling removal (SSR) procedures every year. The majority of these patients suffer for a long time before they are finally referred to us or find us through a friend, a lawyer recommendation, or following an internet search. Many of these patients are assigned diagnoses like refractory urgency, pelvic pain, and interstitial cystitis, and have had a range of therapies offered to them with no durable benefit. To complicate the matter further, some of these patients with complications after MUS have undergone a sling incision to help address their original complaints while leaving some urethral support to protect them from recurrent SUI. Typically, after a sling incision they are deemed to be cured, but some may continue to suffer and undergo unnecessary treatments as not all sling incisions are successful in relieving lower urinary tract symptoms.

The management of MUS complications remains a matter of debate, and the long-term outcome data after removal of MUS is uncertain. Some series have reported that these complications occur at various rates (it is not easy to calculate complication rates in the absence of a registry, which would keep a record of all MUS that are placed), while other series have reported follow-up data on a specific domain such as incontinence, pain, or vaginal mesh exposure. However, this is the first study reporting on mid and long-term outcomes on all presenting complaints ranging from voiding dysfunction to incontinence, pain, dyspareunia, or even recurrent urinary tract infections.

We often struggle with outcome success definition after SSR because the baseline clinical information on the severity and degree of inconvenience of the urinary incontinence before MUS placement is uniquely dependent on patient recall. Rarely do we have access to baseline validated questionnaires or evaluation studies such as urodynamic testing or imaging. Therefore the most commonly used outcome data are based on patient self-report (patient reported outcomes [PRO]). Currently, most published series have just focussed on the rate of recurrent urinary incontinence[7,8] (SUI or urge urinary incontinence [UUI]) or pain[9] after SSR removal while ignoring other aspects of patient complaints such as resolution of pelvic pain and/or dyspareunia, mixed incontinence, and the number of further treatments required. Ideally a ‘cure’ or an ideal outcome in women after SSR should be defined as being “continent, pain-free, sexually active, and not requiring additional medical or surgical therapy”.[10] In order to compare our outcome data with other studies, we were forced to produce an ideal or a cure definition based on a multi-domain or composite PRO report. As the criteria is so stringent, this ideal outcome will bring the success rate down but will allow more uniform reporting.

Clearly, this strict patient-reported definition of success leaves the door open for a large group of women who have improved or need minimally invasive secondary therapies such as a bulking agent for SUI or injection of botulinum toxin for UUI. This is shown in our data, where the ‘cure’ rate only applied to a quarter of our studied group of women, and over half remained in the observation arm. The women in the observed group are not

fully cured, as many still have some mild incontinence, or degree of pelvic pain or dyspareunia. However, after a MUS placement followed by a removal procedure, i.e. two surgical procedures, many would rather opt for observation than undergo yet another corrective surgery with an uncertain outcome, unless intervention was considered 'really' minimally invasive. Time will tell if some of these women will ultimately convert to additional surgical or medical therapies.

REFERENCES

1. Guerette NL et al. Transobturator slings for stress incontinence: using urodynamic parameters to predict outcomes. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(1):97-102.

2. Schierlitz L et al. Effectiveness of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency: a randomized controlled trial. Obstet Gynecol. 2008;112(6):1253-61.

3. Petri E, Ashok K. Comparison of late complications of retropubic and transobturator slings in stress urinary incontinence. Int Urogynecol J. 2012;23(3):321-5.

4. Petri E, Ashok K. Complications of synthetic slings used in female stress urinary incontinence and applicability of the new IUGA-ICS classification. Eur J Obstet Gynecol Reprod Biol. 2012;165(2):347-51.

5. Tommaselli GA et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015;26(9):1253-68.

6. Abouassaly R et al. Complications of tension-free vaginal tape surgery: a multi-institutional review. BJU Int. 2004;94(1):110-3.

7. Giarenis I et al. Management of recurrent stress urinary incontinence after failed midurethral sling: a survey of members of the International Urogynecological Association (IUGA). Int Urogynecol J. 2015;26(9):1285-91.

8. Clifton MM et al. Risk of repeat anti-incontinence surgery following sling release: a review of 93 cases. J Urol. 2014;191(3):710-4.

9. Hou JC et al. Outcome of transvaginal mesh and tape removed for pain only. J Urol. 2014;192(3):856-60.

10. Coskun B et al. Mini-slings can cause complications. Int Urogynecol J. 2015;26(4):557-62.

LONG-TERM OUTCOME OF DORSAL APPROACH IN THE TREATMENT OF CONGENITAL VENTRAL PENILE CURVATURE

Borko Stojanovic,[1] *Marta Bizic,[1] Vladimir Kojovic,[1] Marko Majstorovic,[1] Miroslav L. Djordjevic[1,2]

1. University Children's Hospital, Belgrade, Serbia
2. School of Medicine, University of Belgrade, Belgrade, Serbia
**Correspondence to martabizic@uromiros.com*

Congenital penile curvature (CPC) or chordee is a congenital anomaly that may present as an independent entity or be associated with hypospadias. CPC manifests as a curvature of the penis when in its erect state.[1] The cause of chordee remains unknown, but there are speculations that it is the result of excessive elasticity of one side of the penis compared with the other.[2] Penile curvature associated with hypospadias is mainly ventral and is caused by tethering of the skin, fibrosis, contracture of the fascial tissue surrounding the urethra, and a disproportionately large corpora or a short urethral plate. Penile curvature of >20° is considered significant and surgical repair is the only viable treatment option.[3] Successful correction of the ventral penile curvature requires mobilisation of the neurovascular bundle and dorsal plication of the tunica albuginea.[4–6]

We evaluated 172 patients aged 14–18 years, treated for CPC between January 2002 and December 2006. There were 98 patients with ventral penile curvature associated with hypospadias and 74 with isolated CPC. Correction of CPC was performed under pharmacological erection, induced by prostaglandin E1, to determine the exact point of maximal curvature and to check the result of penile straightening. After cautious mobilisation of the penile neurovascular bundle, curvature correction was performed by dorsal plication corporoplasty using polydioxanone sutures.

In our group of patients the mean follow-up was 10.8 years. All patients were tested for penile length, presence of curvature, quality of erection,

and sensitivity of the glans. Length of the erect penis ranged from 7.2–12.8 cm. Residual ventral curvature was noted in four patients who were initially treated for CPC with hypospadias (4%). One case of recurvature and one of lateral curvature were diagnosed in the second group of 74 patients (2.7%). All patients reported good quality of erection and preserved sensitivity of the glans.

Hypospadias is one of the most common congenital anomalies, with an increasing trend. It can be associated with ventral penile curvature in both severe and distal forms.[3] Independent CPC is also very common among male live births, and thus represents a challenge to classify and correct in particular.[7] The repair of curvature is necessary as CPC can cause potential sexual dysfunction, difficulty, and pain during intercourse, or complete coital incapacity, and if untreated can lead to severe psychological problems.[2,8] Dorsal plication of the tunica albuginea presents a safe and simple method for CPC repair.[5,7] Our data confirm that satisfactory length of the penis and preserved sensation and erection are present with a low rate of recurrence at long-term follow-up.

Acknowledgment: This study is supported by the Ministry of Science and Technical Development, Serbia, Project no. 175048.

REFERENCES

1. Baskin LS et al. Penile curvature. Urology. 1996;48(3):347-56.
2. Makovey I et al. Congenital penile curvature: Update and management. Curr Urol Rep. 2012;13(4):290-7.
3. Stojanovic B et al. Penile curvature incidence in hypospadias: Can it be determined? Adv Urol. 2011;2011:813205.
4. Hayashi Y et al. Modified technique of dorsal plication for penile curvature with or without hypospadias. Urology. 2002;59(4):584-7.
5. Perovic SV et al. A new approach to the treatment of penile curvature. J Urol. 1998;160(3 Pt 2):1123-7.
6. Perovic SV et al. The penile disassembly technique in hypospadias repair. Br J Urol. 1998;81(3):479-87.
7. Lee SS et al. Congenital penile curvature: long-term results of operative treatment using the plication procedure. Asian J Androl. 2004;6(3):273-6.
8. Zachalski W et al. Evaluation of the treatment of congenital penile curvature including psychosexual assessment. J Sex Med. 2015;12(8):1828-35.

THE PREHISTORIC PENIS

***Javier Angulo**

Department of Urology,
Universidad Europea de Madrid, Madrid, Spain
**Correspondence to jangulo@futurnet.es*

Although human depictions are scarce in prehistory, i.e. preceding our first records of written language, both male and female genital representations are relatively common motives; they are depicted at prehistoric times all over the world on cave walls, rock shelters, and pieces derived from excavations of archaeological sites of stone, bone, and antler portable material and decoration. The most common representations date from the Upper Palaeolithic period (approximately 40,000–12,000 years before present [BP]) and appear more numerous in Western Europe, especially Iberia and France. These graphical elements suggest that early modern humans (*Homo sapiens*) had an awareness of the physiological phenomena (erection, copulation, ejaculation, and orgasm) related to sexuality and reproduction (Figure 1), and of the related pathological processes (phimosis, paraphimosis, urethral discharge, and genital mass). Indirect evidence exists that suggests foreskin retraction and/or circumcision was also performed, and a detailed analysis suggests that other penile decoration rituals (tattooing, piercing, and scarification) were performed. These were possibly done as group recognition strategies, mainly during the Upper Magdalenian period (11,000–12,700 years BP), representing one of the oldest known anthropological registries of body decoration. Circumcised and decorated phalli currently constitute the earliest records of human anatomical instrumentation and thus imply the existence of surgical knowledge during the late prehistoric period.

Human and animal erection captivated the artists' minds and possibly implied virility and strength, opposed not to the feminine, but to nature itself.

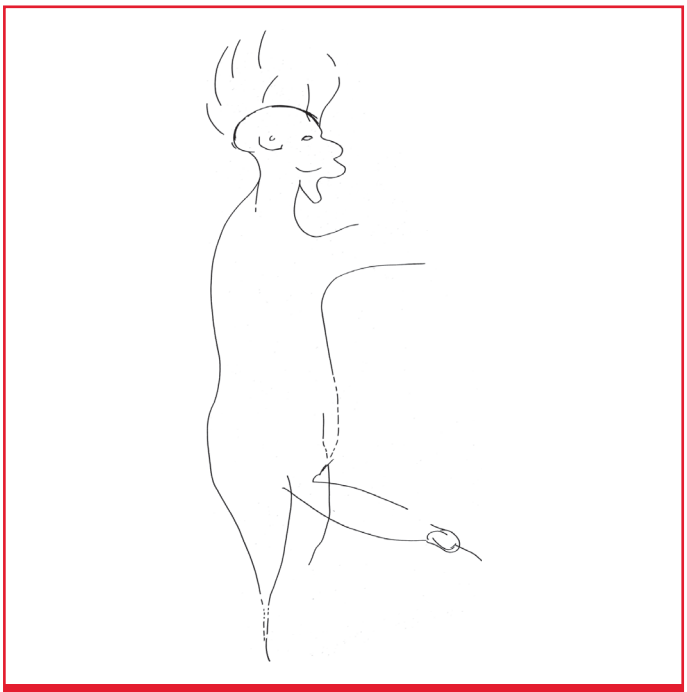


Figure 1: Ejaculating human represented in the open air site of Ribera do Piscos (Vilanova de Foz Côa, Portugal). A large size male figure reveals seminal emission and male orgasm with open mouth and lines coming out from his head.

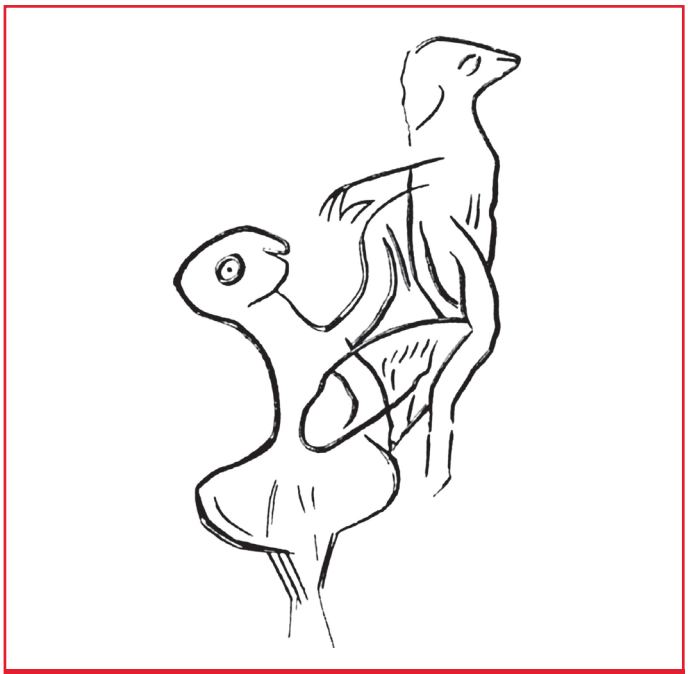


Figure 2: Coital scene represented in Cueva de Los Casares (Riba de Saelices, Spain). A human couple facing each other and the male figure displays an enormous penis placed on the pubis of the female figure.

Many ithyphallic men were depicted as partly animal and partly human. In several instances, male erection was associated with serious danger or death, and could be interpreted as part of a shamanistic representation linked to the loss of the soul. Many portable art elements are made of antler or bone and have the form and size of the penis. Although their specific use is unknown, it is clear that they were precious elements because the materials could instead have been used to produce spear points, pendants, or even needles. The complementation between male and female genitalia is also a constant, and was sometimes explicitly represented in the form of a human or animal coital scene (Figure 2). The positions are varied and, although infrequent, may represent a 'Kamasutra-like' guide. Mating was rarely linked to childbearing representation, which implies knowledge of contraceptive practice. In a curious post-Palaeolithic carving in an open-air site in the Côa Valley, Portugal, a condom-like object is represented. In Neolithic Europe (9,000 years BP), the penis was often evident on male figures depicted on rock shelters but with less anatomical detail than in naturalistic Palaeolithic art.

Agriculture led to male dominance and female genitals were less frequently depicted. The penis is recognised in stone sculptures of possible ritual use, like the phallic collection in the Gozo Museum of Archaeology, Malta. Evidence from the Copper age (5,500 years BP) implies a widespread monumental use of the penis form in numerous menhirs all over the Atlantic shore, and in schematic shelter wall art in the mountainous landscape of Southern Europe; these symbolic human figures often have a prominent penis. Penile representation in fine carving during the late Bronze-Iron age (3,000–2,500 years BP) suggests penile infibulation. This form of penile mutilation prevented warriors from losing their energy in penetration and has been performed in many tribes of modern primitives. In conclusion, penis depiction during prehistory has constantly evolved and many clues can be obtained in the absence of written language when attention is paid to this source of knowledge.

EDITOR'S PICK

In this review, Wei Jin and colleagues from the University of Missouri-Kansas City, Missouri, USA, have summarised the ligands associated with prostate-specific membrane antigen (PSMA), which is a widely used biomarker and antigen in prostate cancer diagnosis. This topic is one of the most attractive and promising subjects in the diagnosis and therapy of prostate cancer, and will be of great interest to our readers.

Dr A. Erdem Canda

PSMA-SPECIFIC LIGANDS IN PROSTATE CANCER DIAGNOSIS AND THERAPY

Wei Jin, Ashutosh Barve, *Kun Cheng

Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri–Kansas City, Kansas City, Missouri, USA
**Correspondence to chengkun@umkc.edu*

Disclosure: The authors have declared no conflicts of interest.
Received: 17.11.2015 **Accepted:** 06.01.2016
Citation: EMJ Urol. 2016;4[1]:62-69.

ABSTRACT

Prostate-specific membrane antigen (PSMA) is the most extensively studied biomarker and antigen of prostate cancer. It is overexpressed in almost all prostate cancers, and the expression level increases with prostate cancer progression. PSMA is also highly expressed in the neovasculature of solid tumours including prostate cancer. As a result, numerous PSMA-specific ligands have been discovered for prostate cancer diagnosis and therapy, and one of them has been approved for clinical use. Moreover, a number of other PSMA-specific ligands are currently evaluated in clinical studies. In this review we discuss four major types of PSMA-specific ligands, including antibody, aptamer, peptide, and small molecule inhibitor. Their emerging applications in prostate cancer diagnosis, targeted drug delivery, and therapy are also discussed.

Keywords: Prostate-specific membrane antigen (PSMA), diagnosis, targeted drug delivery, antibody, aptamer, peptide.

INTRODUCTION

Prostate cancer is the most common male malignancy and the second-leading cause of cancer death in American men. Current therapies for prostate cancer include surgery, chemotherapy, cryosurgery, radiation, and hormonal therapy. These approaches are used either as monotherapy or in combination according to stages in the patients. A variety of prostate cancer specific antigens have been explored for targeted drug delivery and diagnosis. Among them, prostate-specific membrane antigen (PSMA) is the most extensively studied biomarker and antigen of prostate cancer.[1]

PSMA, also known as folate hydrolase, N-acetyl-α-linked acidic dipeptidase I, or glutamate carboxypeptidase II, is a Type 2 transmembrane glycosylated protein. Belonging to the group of zinc-dependent exopeptidases with a binuclear zinc site, PSMA contains a glycosylated extracellular domain of 707 amino acids, a transmembrane domain of 24 amino acids, and an intracellular domain of 19 amino acids.[1] The crystal structure of PSMA reveals a symmetric dimer with each polypeptide chain containing three functional and structural domains: a C-terminal/helical domain, an apical domain, and a protease domain.[2,3] Although the exact physiologic function of PSMA

in the prostate is not fully understood, it is known that PSMA can cleave g-linked glutamates from polyglutamated folates (known as folate hydrolase activity) and α-linked glutamate from N-acetyl aspartyl glutamate (known as NAALADase activity).[4]

PSMA is expressed in normal prostate epithelial cells, but its expression level in prostate cancer cells is much higher. Notably, PSMA is overexpressed in almost all prostate cancers, and the expression level increases with disease progression.[1,5] Moreover, PSMA is overexpressed in the neovasculature of solid tumours, but not in normal tissue vasculature. PSMA expression is also detectable in several normal tissues, such as the small intestine, proximal renal tubules, and salivary glands,[6] but the expression level of PSMA in prostate cancers is approximately 100 to 1000-fold higher.[7,8] In addition, the site of PSMA expression in normal tissues (brush border/luminal location) is not exposed to direct blood circulation, leading to negligible interaction between PSMA-specific ligands and PSMA in normal tissues.[1,8] As a result, PSMA has been recognised as the most valuable prostate cancer-specific antigen for prostate cancer diagnosis and therapy. The aim of this review is therefore to discuss the currently available PSMA-specific ligands (antibody, single chain fragment variable [scFv], aptamer, peptide, and small molecule) that have been explored for prostate cancer diagnosis and therapy (Figure 1).

PSMA-Specific Antibody and scFv

Antibody is by far the most common type of PSMA-specific ligand in preclinical and clinical studies. PSMA was initially identified by the murine monoclonal antibody (mAb) 7E11, which was discovered after immunisation of mice with preparations of PSMA-positive LNCaP cells.[9] The mAb 7E11 has thereafter been used as the first anti-PSMA antibody for various prostate cancer treatments and diagnoses. For example, ProstaScint® (^{111}Indium-labelled mAb7E11) was approved by the FDA for the imaging of prostate cancer.[10,11,12] However, mAb 7E11 binds to the intracellular domain of PSMA and therefore cannot bind viable prostate cancer cells, thus limiting its potential clinical applications.[13] Consequently, numerous efforts have been made to discover other mAbs targeting the extracellular domain of PSMA.

Using hybridoma technology, Bander and co-workers firstly discovered four mAbs (J59l, J533, J415, and E99) that specifically bind to the extracellular domain of PSMA with K_d values in the low nM range (1.76–18 nM).[14,15] Later, these PSMA-specific mAbs were labelled with ^{131}I and ^{111}In for imaging studies in nude mice bearing LNCaP xenograft. These mAbs exhibit higher tumour uptake compared with radiolabelled 7E11. Moreover, 7E11 tends to accumulate in the areas of necrosis, whereas J591 and J415 mainly accumulate in viable tumours, suggesting the great therapeutic potential of mAbs in targeting the PSMA extracellular domain.[16] Since then, several other groups have discovered numerous PSMA mAbs that target the extracellular domain of PSMA. All these mAbs show high affinity to purified PSMA as well as viable prostate cancer cells.[17,18]

Among the mAbs shown to target the PSMA extracellular domain, mAb J591 has attracted the most attention as an anti-PSMA antibody for prostate cancer diagnosis and therapy because of its high affinity and specificity to PSMA. Several J591-based imaging and therapeutic agents are currently being evaluated in clinical trials. For example, ^{89}Zr-labelled J591 was developed as a positron emission tomography (PET) imaging agent to detect metastatic castration-resistant prostate cancer cells. The Phase I/II study reveals superior targeting of bone lesions compared with conventional imaging modalities or a combination of conventional imaging modalities.[19] In another Phase II clinical trial, ^{177}Lutetium-labelled J591 exhibits high tolerance, accurate tumour targeting, and dose-dependent prostate-specific antigen responses in metastatic castration-resistant prostate cancer patients, suggesting its promising potential of targeting cytotoxic agents to PSMA.[20] ^{177}Lutetium-J591 in combination with docetaxel is in an ongoing Phase Iclinical study to evaluate its effectiveness against metastatic, castrate-resistant prostate cancer (Clinical Trial NCT00916123).

mAb J591 has also been conjugated to the cytotoxic agent monomethyl auristatin E through a valine-citrulline spacer to form an antibody drug conjugate (ADC).[21] The J591-based ADC exhibits very high cytotoxicity (IC_{50} <0.022 nM) in PSMA-positive cell lines, but much less cytotoxicity (IC_{50} >30 nM) in PSMA-negative cells.[21] The ADC dramatically reduces the size of docetaxel-refractory xenograft prostate tumours, including tumours larger than 700 mm^3. Moreover, the survival rate of the ADC treated group is noticeably higher than that of the docetaxel treated group.[21] The J591-based ADC is currently under evaluation

in a Phase II clinical trial. In addition to radiolabelled mAb and ADC, mAb J591 was used as a targeting ligand in the PEGylated liposome loaded with alpha-particle generator nuclide ^{225}Ac as the anti-cancer agent. The J591-labelled liposome specifically binds to several PSMA-positive cell lines and accordingly induces cell apoptosis.[22]

Wetterauer et al.[17] discovered three other PSMA-specific mAbs (3/E7, 3/F11, 3/A12) from mice immunised with unpurified LNCaP lysate. These mAbs demonstrate high affinity to purified PSMA, viable LNCaP cells, and PSMA-transfected cells. Further studies showed that these three mAbs bind to different extracellular PSMA epitopes. Moreover, the mAbs 3/E7, 3/F11, and 3/A12 exhibit a similar binding affinity to J591 in C4-2 cells.[23] The mAbs 3/E7, 3/F11, and 3/A12 were labelled with ^{64}Cu and evaluated in mice bearing prostate cancer xenografts using microPET. The imaging results reveal high uptake of the mAbs in PSMA-positive C4-2 xenograft at 24 and 48 hours post-administration but not in PSMA-negative DU-145 xenografts.[24] The mAb 3/F11 was also evaluated as a radioimmunotherapeutic agent after labelling with ^{177}Lu. The ^{177}Lu labelled 3/F11 exhibits high uptake in C4-2 xenografts with a serum half-life of 7 days. A biodistribution study demonstrated maximum uptake in the tumour at 72 hours post-administration. Furthermore, a single dose of ^{177}Lu-DOTA-3/F11 inhibits tumour growth and improves the survival rate of the mice, indicating the great potential of using 3/F11 as a targeting ligand for prostate cancer therapeutics.[25]

Instead of immunising animals and using hybridoma technology to discover mAbs, scFv phage display has also been used to identify anti-PSMA antibody fragments. In one study, a scFv phage library was constructed from the hybridoma of the mAb 3/A12, which targets the PSMA extracellular domain. The scFv A5 was identified after several rounds of biopanning on LNCaP cells and purified PSMA, and exhibits high affinity to LNCaP cells with a K_d of 38 nM.[26] A recombinant immunotoxin (A5-PE40) containing the toxic domain of Pseudomonas Exotoxin A (PE40) and scFv A5 was then constructed, and showed a very high cytotoxicity in LNCaP cells (IC_{50}=20 pM).[26] The same approach was also used to discover another anti-PSMA scFv D7 from the phage library that was constructed from the hybridoma 3/F11. Similarly, the recombinant immunotoxin (D7-PE40) shows high affinity to C4-2 cells and induces cell apoptosis with an IC50 of 140 pM.[27] The immunotoxin D7-PE40 significantly reduces the size of established C4-2 xenografts in mice. Meanwhile, the immunotoxin D7-PE40 is well tolerated in mice up to a dose of 20 µg.[27]

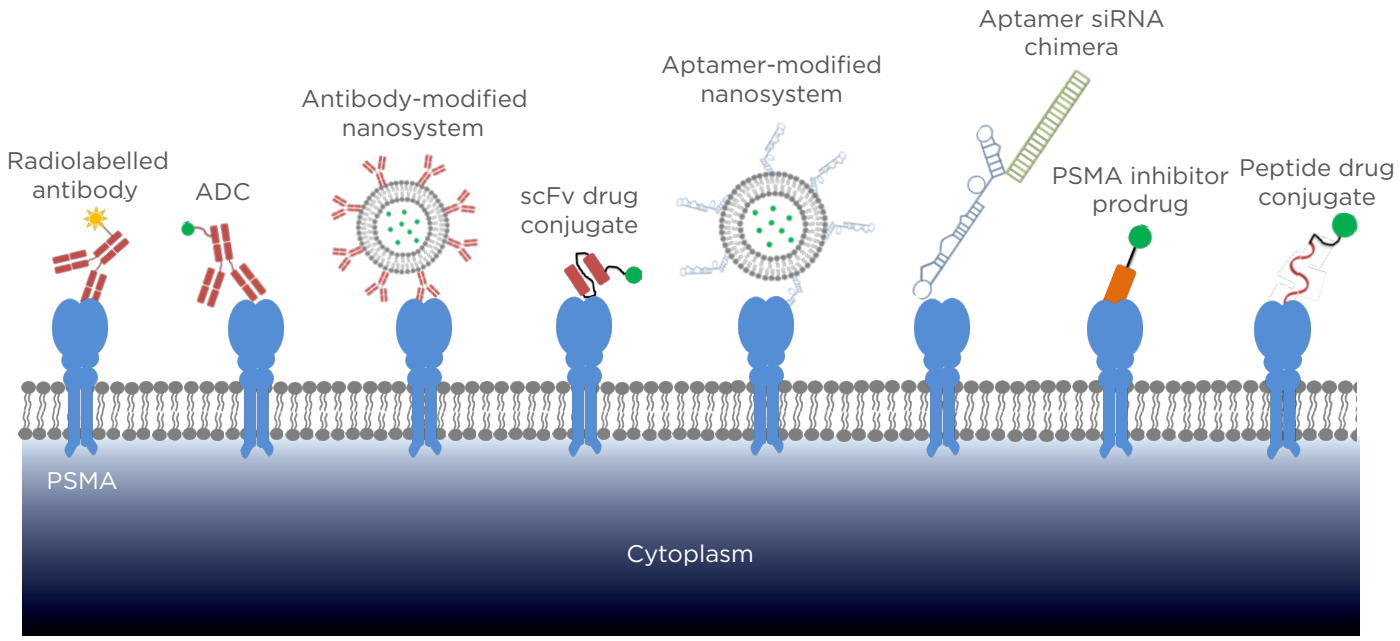


Figure 1: Targeting strategies of PSMA-specific ligands in prostate cancer diagnosis and therapy.
PSMA: prostate-specific membrane antigen; ADC: antibody drug conjugate; scFv: single chain fragment variable; siRNA: small interfering RNA.

Prostate Cancer-Specific Aptamer

Aptamers are single-stranded oligonucleotides that have high affinity to various molecular moieties. Aptamers can be identified through the systematic evolution of ligands by exponential enrichment (SELEX) from a large pool of random oligonucleotide sequences.[28] Using SELEX against the PSMA extracellular domain, Lupold and co-workers[29] identified two 40-mer RNA aptamers, termed xPSM-A9 and xPSM-A10, with low nanomolar affinity. The aptamers xPSM-A9 and xPSM-A10 also inhibit the NAALADase activity of PSMA with a K_i of 2.1 nM and 11.2 nM, respectively.[29]

Due to its high affinity and specificity to PSMA, the aptamer xPSM-A10 was radiolabelled with ^{64}Cu and used as a PET imaging agent for targeted molecular imaging of prostate cancer.[30] Moreover, the PSMA aptamers have been widely used for prostate cancer targeted drug delivery systems. For example, the aptamer xPSM-A9 was adopted as a PSMA-specific ligand and conjugated to the surface of a liposome encapsulating doxorubicin.[31] The aptamer-conjugated liposomes specifically internalise into PSMA-positive LNCaP cells and subsequently induce cell apoptosis, while neither uptake nor cytotoxicity is observed in PSMA-negative PC-3 cells. A biodistribution study demonstrated high accumulation of doxorubicin in tumour sites at 12 and 24 hours after intravenous administration. Accordingly, an enhanced anti-cancer effect was observed in the animals treated with the A9-conjugated liposome.[31]

Similarly, PSMA aptamers have been used in small interfering RNA (siRNA) delivery for prostate cancer therapy. Since the discovery of RNA interference, siRNAs have attracted much attention as novel therapeutic agents to treat various diseases. However, lack of efficient delivery systems is still the major hurdle that limits the clinical translation of siRNA. In an exploratory study of siRNA delivery, the A10 aptamer was directly linked to an siRNA to form the aptamer–siRNA chimera to achieve targeted delivery to PSMA-positive prostate cancers.[32] The A10 aptamer-siRNA chimera not only shows selective uptake in PSMA-positive cancer cells *in vitro* but also demonstrates significant inhibition of LNCaP xenograft tumour growth *in vivo*. This is one of the few pioneering studies showing the *in vivo* activity of siRNA in animal studies.[32]

The PSMA aptamer was also explored as a therapeutic agent against advanced prostate cancer because several studies have suggested that PSMA's enzymatic activity may play important roles in prostate cancer angiogenesis, progression, and metastasis.[4,33] In one such study, the PSMA-specific aptamer A9g (truncated form of the aptamer A9) specifically inhibits the migration and invasion of PSMA-positive prostate cancer cells *in vitro*. A further animal study of the aptamer A9g reveals potent inhibition of metastasis in a xenograft mouse model of metastatic prostate cancer. Data from this study suggest that PSMA inhibitors could be used alone as emerging therapeutic agents for advanced prostate cancer.[34]

Given the poor stability of RNA molecules under physiological condition, DNA aptamer targeting PSMA was discovered to overcome the poor stability of RNA aptamer. A 48-mer anti-PSMA DNA aptamer (SZTI01) containing a binding site for doxorubicin was identified using SELEX against PSMA. A dimeric form of the aptamer SZTI01 was constructed to form a complex with doxorubicin. The aptamer/doxorubicin complex is stable at physiological conditions and specifically binds to PSMA-positive C4-2 cells. The complex also induces high cytotoxicity in C4-2 cells but negligible activity in PSMA-null cells, indicating its high selectivity for PSMA-positive cells.[35]

Prostate Cancer-Specific Peptide

Peptide phage display technology has been widely used for identification of peptide ligands against various molecular targets including cancer-specific antigens. Compared with aptamer and antibody ligands, peptide ligands have several advantages, such as low molecular weight, high permeability, low immunogenicity, ease of synthesis, and flexibility in chemical conjugation.[36,37] As a result, a great deal of interest has been focussed on the identification of PSMA-specific peptides. For example, biopanning against a recombinant PSMA extracellular domain was utilised to identify a PSMA-specific peptide that can efficiently inhibit the enzymatic activity of PSMA with an IC_{50} of 26 μM. A dimeric form of this peptide further increases its binding affinity to PSMA.[38] In another study, whole-cell biopanning against PSMA-positive LNCaP cells was conducted to identify an LNCaP-specific peptide (KYL), which can efficiently deliver various cargos to LNCaP cells. Although the KYL peptide shows high and specific binding to LNCaP cells but not to PSMA-negative PC-3 cells, the peptide is not PSMA-specific and its

target moiety is unknown.[39] We recently designed a combinatorial biopanning strategy against a recombinant PSMA extracellular domain, LNCaP cells, and LNCaP xenografts in nude mice and identified a PSMA-specific peptide (GTI), which shows high affinity to PSMA-positive cells *in vitro* and *in vivo*. The K_d values of the GTI peptide to LNCaP and C4-2 cells are 8.22 and 8.91 µM, respectively (unpublished data). One potential problem that may limit the application of peptide ligands is their relative low binding affinity compared with antibodies and aptamers. Most peptides identified from phage display show K_d values in the low micromolar range.[40] Therefore, further modification of peptide ligands, such as D-form amino acid modification,[41] ligand dimerisation, and tetramerisation[38] may be used to further improve their affinity.

Table 1: Applications of prostate-specific membrane antigen-specific ligands in prostate cancer imaging.

Targeting ligands	Imaging agents	Phase status	Reference
mAb 7E11	^{111}In	Commercially available	10-12
mAb J591	^{89}Zr	Phase II	19
mAb 3/E7, 3/F11, 3/A12	^{64}Cu	Preclinical	24
xPSM-A10	^{64}Cu	Preclinical	30
MIP-1095, 1072	^{131}I, ^{123}I	Phase I	48
MIP-1404, 1405	^{99m}Tc	Phase II	45
DCFBC	^{18}F	Phase I & II	53
DUPA	^{99m}Tc	Preclinical	54
Glu-NH-CO-NH-Lys(Ahx)-HBED-CC	^{68}Ga	Phase II	51,52
Phosphoramidate peptidomimetic	^{18}F	Preclinical	55

mAb: monoclonal antibody.

Table 2: Applications of PSMA-specific ligands in prostate cancer therapy.

Targeting ligands	Therapeutic agents	Delivery system	Phase status	Reference
mAb J591	^{177}Lu-labelled	Radiolabelling antibody	Phase II	20
mAb J591	Monomethyl auristatin E	Antibody drug conjugate	Phase II	21
mAb J591	^{177}Lu-labelled	Combination with docetaxel	Phase I	NCT00916123*
mAb J591	^{177}Lu-labelled	Combination with ketoconazole and hydrocortisone	Phase II	NCT00859781*
mAb J591	^{225}Ac	Liposome	Preclinical	22
mAb 3/F11	^{177}Lu-labelled	Radiolabelling antibody	Preclinical	25
scFv fragment A5 scFv fragment D7	*Pseudomonas* exotoxin A (PE40)	Recombinant immunotoxin	Preclinical	26-27
xPSM-A9	Doxorubicin	Liposome	Preclinical	31
xPSM-A10	PLK1 siRNA and BCL2 siRNA	Aptamer siRNA chimeras	Preclinical	32
xPSM-A9 derivative	xPSM-A9 derivative	Aptamer alone	Preclinical	34
DNA aptamer	Doxorubicin	Dimeric aptamer doxorubicin conjugate	Preclinical	35
PSMA inhibitor DUPA	TubH	Prodrug	Preclinical	54

*ClinicalTrials.gov Identifier (www.ClinicalTrials.gov)
mAb: monoclonal antibody; PSMA: prostate-specific membrane antigen; scFv: single chain fragment variable; siRNA: small interfering RNA.

Prostate Cancer-Specific Small Molecule

N-acetyl-L-aspartyl-L-glutamate (NAAG) is an endogenous peptide found in the mammalian nervous system. It can be hydrolysed by the N-acetylated α-linked acidic dipeptidase (NAALADase, or NAAG peptidase) with a K_m of 540 nM.[42] Given the fact that PSMA is highly homologous to NAAG peptidase, several studies have been carried out to design NAAG analogues that can specifically bind to PSMA.[43-46]

Based on their previous experience in designing NAAG analogues, Pomper et al.[43] synthesised two radiolabelled small molecules, [^{11}C]DCMC and [^{125}I]DCIT. Both of these analogues exhibit high accumulation in LNCaP xenograft at 30 minutes post-administration, whereas the uptake in PSMA-negative MCF-7 and PC-3 derived tumours is negligible. Another group synthesised a series of glutamate-urea-X (X is a derivatised lysine) heterodimeric inhibitors with high affinity to PSMA in the low nM range.[44] Two of the inhibitors, MIP-1072 and MIP-1095, efficiently inhibit PSMA enzymatic activity with K_i values of 4.6 nM and 0.24 nM, respectively. Moreover, MIP-1072 and MIP-1095 exhibit very high affinity to PSMA (K_d <4 nM).[47] Specific binding of ^{125}I labelled MIP-1072 and MIP-1095 was demonstrated in mice bearing LNCaP xenografts.[47] These promising data have led to the Phase I clinical trial of these small molecule inhibitors for imaging prostate cancer.[48] Clinical studies demonstrate that ^{123}I-MIP-1072 and ^{123}I-MIP-1095 can detect lesions in the prostate gland, soft tissues, and bones at 1–4 hours post-injection. Target-to background ratio is >10:1 at 4 and 24 hours for single photon emission computed tomograph/computed tomography (SPECT/CT).[48] Two other PSMA small molecule inhibitors, MIP-1404 and 1405, also show high affinity to LNCaP cells with K_d values of 1.07 nM and 4.35 nM, respectively.[46] A clinical study of (99m)Tc-MIP-1404 and 1405 revealed that they can detect soft-tissue prostate cancer lesions including subcentimetre lymph nodes and most bone metastatic lesions.[45]

It is reported that the active binding site of PSMA is composed of one binding pocket for glutamate-urea-X inhibitors and another lipophilic pocket.[49] Eisenhut et al.[50] therefore hypothesised that attachment of a hydrophobic moiety to the current glutamate-urea based PSMA inhibitors may enhance their affinity to PSMA. As a result, a novel imaging agent was synthesised by conjugating a hydrophobic side chain, ^{68}Ga chelator-HBED-CC (N,N'-bis[2-hydroxy-5(carboxyethyl)benzyl ethylenediamine-N,N'-diacetic acid), to a glutamate-urea based inhibitor. The new imaging agent exhibits enhanced specificity for PSMA-positive tumour cells *in vitro* and *in vivo*. It also demonstrates faster blood and organ clearances and lower liver accumulation in an animal study.[50] The [^{68}Ga] PSMA-HBED-CC-PET/CT imaging agent has also been evaluated in prostate cancer patients for the diagnosis, radiotherapy, and management of prostate cancer.[51,52] Several other small molecule inhibitors, such as DUPA, DCFBC, and phosphoramidate peptidomimetic have also entered preclinical and clinical studies as imaging agents to detect castration-resistant prostate and metastatic hormone-naïve prostate cancer.[53-55]

Due to their high affinity and specificity to PSMA, these PSMA small molecule inhibitors have also been investigated for prostate cancer targeted drug delivery. In one study, Low et al.[54] conjugated tubulysin, a microtubule inhibitor, to DUPA, a small molecule inhibitor of PSMA with a K_d value of 14 nM. The conjugated drug (DUPA-TubH) exhibits high anti-cancer activity against PSMA-positive prostate cancer cells *in vitro* and *in vivo*. Pre-administration of excess PSMA inhibitors abolishes the activity of DUPA-TubH, indicating the high specificity of DUPA-TubH to PSMA. Later, the same group conjugated a series of different chemotherapeutic agents to DUPA and similar activity against PSMA-positive prostate cancer was observed, suggesting flexibility in the use of the PSMA small molecule inhibitor as a targeting ligand for various agents.[56] A number of other PSMA-specific small molecules have also been explored as targeting ligands for various therapeutic agents, including radionuclide,[57] gold nanoparticles,[58] photosensitiser,[59] and polymeric microbubbles.[60]

CONCLUSION

Four types of PSMA-specific ligands and their applications in prostate cancer imaging (Table 1) and therapy (Table 2) are discussed in the review. Although PSMA-specific ligands are mainly used as prostate cancer imaging agents and targeting ligands for drug delivery systems, some of the PSMA inhibitors can also be used alone as anti-cancer therapeutic agents.

As the first generation PSMA-specific ligand, PSMA mAbs have been widely investigated because of their high affinity and specificity. One of the PSMA mAbs, ProstaScint®, was approved by the FDA

for imaging prostate cancer. Several other PSMA mAbs are currently in clinical trials to explore their application as imaging and therapeutic agents. Regardless of its success, the major disadvantages of mAbs are possible immunogenicity, long half-life in the circulation, and low permeability in tumour site due to their large molecular size. As a result, other PSMA ligands with small sizes, such as aptamers, peptides, and small molecule inhibitors have gained much interest in recent years in prostate cancer diagnosis and targeted therapy.

Taken together, a great deal of effort has been devoted to discovering numerous PSMA-specific ligands and exploring their applications in prostate cancer diagnosis and therapy in the past two decades. Although the majority of these applications focus on the imaging of prostate cancer, there is an increasing interest in the use of the ligands in targeted drug delivery systems to increase the efficacy of current prostate cancer therapeutic agents.

REFERENCES

1. Barve A et al. Prostate cancer relevant antigens and enzymes for targeted drug delivery. J Control Release. 2014;187: 118-32.

2. Davis MI et al. Crystal structure of prostate-specific membrane antigen, a tumor marker and peptidase. Proc Natl Acad Sci U S A. 2005;102(17):5981-6.

3. Bukrinsky JT et al. Native carboxypeptidase A in a new crystal environment reveals a different conformation of the important tyrosine 248. Biochemistry. 1998;37(47):16555-64.

4. Yao V et al. Expression of prostate-specific membrane antigen (PSMA), increases cell folate uptake and proliferation and suggests a novel role for PSMA in the uptake of the non-polyglutamated folate, folic acid. Prostate. 2010;70(3):305-16.

5. Sweat SD et al. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology. 1998;52(4):637-40.

6. Troyer JK et al. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer. 1995;62(5):552-8.

7. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91(3): 528-39.

8. Akhtar NH et al. Prostate-specific membrane antigen-based therapeutics. Adv Urol. 2012;2012:973820.

9. Horoszewicz JS et al. Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients. Anticancer Res. 1987;7(5B):927-35.

10. Petronis JD et al. Indium-111 capromab pendetide (ProstaScint) imaging to detect recurrent and metastatic prostate cancer. Clin Nucl Med. 1998;23(10):672-7.

11. Hinkle GH et al. Multicenter radioimmunoscintigraphic evaluation of patients with prostate carcinoma using indium-111 capromab pendetide. Cancer. 1998;83(4):739-47.

12. Rosenthal SA et al. Utility of capromab pendetide (ProstaScint) imaging in the management of prostate cancer. Tech Urol. 2001;7(1):27-37.

13. Troyer JK et al. Biochemical characterization and mapping of the 7E11-C5.3 epitope of the prostate-specific membrane antigen. Urol Oncol. 1995;1(1):29-37.

14. Liu H et al. Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumor vascular endothelium. Cancer Res. 1997;57(17):3629-34.

15. Smith-Jones PM et al. In vitro characterization of radiolabeled monoclonal antibodies specific for the extracellular domain of prostate-specific membrane antigen. Cancer Res. 2000;60(18):5237-43.

16. Smith-Jones PM et al. Radiolabeled monoclonal antibodies specific to the extracellular domain of prostate-specific membrane antigen: preclinical studies in nude mice bearing LNCaP human prostate tumor. J Nucl Med. 2003;44(4):610-7.

17. Elsässer-Beile U et al. A new generation of monoclonal and recombinant antibodies against cell-adherent prostate specific membrane antigen for diagnostic and therapeutic targeting of prostate cancer. Prostate. 2006;66(13):1359-70.

18. Grauer LS et al. Identification, purification, and subcellular localization of prostate-specific membrane antigen PSM' protein in the LNCaP prostatic carcinoma cell line. Cancer Res. 1998;58(21):4787-9.

19. Pandit-Taskar N et al. A Phase I/II Study for Analytic Validation of 89Zr-J591 ImmunoPET as a Molecular Imaging Agent for Metastatic Prostate Cancer. Clin Cancer Res. 2015. [Epub ahead of print].

20. Tagawa ST et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res. 2013;19(18):5182-91.

21. Wang X et al. In vitro and in vivo responses of advanced prostate tumors to PSMA ADC, an auristatin-conjugated antibody to prostate-specific membrane antigen. Mol Cancer Ther. 2011;10(9): 1728-39.

22. Bandekar A et al. Anti-prostate-specific membrane antigen liposomes loaded with 225Ac for potential targeted antivascular alpha-particle therapy of cancer. J Nucl Med. 2014;55(1):107-14.

23. Wolf P et al. Three conformational antibodies specific for different PSMA epitopes are promising diagnostic and therapeutic tools for prostate cancer. Prostate. 2010;70(5):562-9.

24. Alt K et al. High-resolution animal PET imaging of prostate cancer xenografts with three different 64Cu-labeled antibodies against native cell-adherent PSMA. Prostate. 2010;70(13):1413-21.

25. Behe M et al. In vivo testing of 177Lu-labelled anti-PSMA antibody as a new radioimmunotherapeutic agent against prostate cancer. In Vivo. 2011;25(1):55-9.

26. Wolf P et al. A recombinant PSMA-specific single-chain immunotoxin has potent and selective toxicity against prostate cancer cells. Cancer Immunol Immunother. 2006;55(11):1367-73.

27. Wolf P et al. Preclinical evaluation of a recombinant anti-prostate specific membrane antigen single-chain immunotoxin against prostate cancer. J Immunother. 2010;33(3):262-71.

28. Fitzwater T, Polisky B. A SELEX primer. Methods Enzymol. 1996;267:275-301.

29. Lupold SE et al. Identification and characterization of nuclease-stabilized RNA molecules that bind human prostate cancer cells via the prostate-specific membrane antigen. Cancer Res. 2002;62(14):4029-33.

30. Rockey WM et al. Synthesis and

radiolabeling of chelator-RNA aptamer bioconjugates with copper-64 for targeted molecular imaging. Bioorg Med Chem. 2011;19(13):4080-90.

31. Baek SE et al. RNA aptamer-conjugated liposome as an efficient anticancer drug delivery vehicle targeting cancer cells in vivo. J Control Release. 2014;196:234-42.

32. McNamara JO et al. Cell type-specific delivery of siRNAs with aptamer-siRNA chimeras. Nat Biotechnol. 2006;24(8):1005-15.

33. Conway RE et al. Prostate-specific membrane antigen regulates angiogenesis by modulating integrin signal transduction. Mol Cell Biol. 2006;26(14):5310-24.

34. Dassie JP et al. Targeted inhibition of prostate cancer metastases with an RNA aptamer to prostate-specific membrane antigen. Mol Ther. 2014;22(11):1910-22.

35. Boyacioglu O et al. Dimeric DNA Aptamer Complexes for High-capacity-targeted Drug Delivery Using pH-sensitive Covalent Linkages. Mol Ther Nucleic Acids. 2013;2:e107.

36. Chen Z et al. Discovery of Peptide ligands for hepatic stellate cells using phage display. Mol Pharm. 2015;12(6): 2180-8.

37. Shukla RS et al. Peptides used in the delivery of small noncoding RNA. Mol Pharm. 2014;11(10):3395-408.

38. Aggarwal S et al. A dimeric peptide that binds selectively to prostate-specific membrane antigen and inhibits its enzymatic activity. Cancer Res. 2006;66(18):9171-7.

39. Qin B et al. Identification of a LNCaP-specific binding peptide using phage display. Pharm Res. 2011;28(10):2422-34.

40. Hao J et al. Identification and rational redesign of peptide ligands to CRIP1, a novel biomarker for cancers. PLoS Comput Biol. 2008;4(8):e1000138.

41. Chen S et al. Improving binding affinity and stability of peptide ligands by substituting glycines with D-amino acids. Chembiochem. 2013;14(11):1316-22.

42. Robinson MB et al. Hydrolysis of the brain dipeptide N-acetyl-L-aspartyl-L-glutamate. Identification and characterization of a novel N-acetylated alpha-linked acidic dipeptidase activity from rat brain. J Biol Chem. 1987;262 (30):14498-506.

43. Foss CA et al. Radiolabeled small-molecule ligands for prostate-specific membrane antigen: in vivo imaging in experimental models of prostate cancer. Clin Cancer Res. 2005;11(11):4022-8.

44. Maresca KP et al. A series of halogenated heterodimeric inhibitors of prostate specific membrane antigen (PSMA) as radiolabeled probes for targeting prostate cancer. J Med Chem. 2009;52(2):347-57.

45. Vallabhajosula S et al. 99mTc-labeled small-molecule inhibitors of prostate-specific membrane antigen: pharmacokinetics and biodistribution studies in healthy subjects and patients with metastatic prostate cancer. J Nucl Med. 2014;55(11):1791-8.

46. Hillier SM et al. 99mTc-labeled small-molecule inhibitors of prostate-specific membrane antigen for molecular imaging of prostate cancer. J Nucl Med. 2013;54(8):1369-76.

47. Hillier SM et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17):6932-40.

48. Barrett JA et al. First-in-man evaluation of 2 high-affinity PSMA-avid small molecules for imaging prostate cancer. J Nucl Med. 2013;54(3):380-7.

49. Kularatne SA et al. Design, synthesis, and preclinical evaluation of prostate-specific membrane antigen targeted (99m)Tc-radioimaging agents. Mol Pharm. 2009;6(3):790-800.

50. Eder M et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem. 2012;23(4):688-97.

51. Sahlmann CO et al. Biphasic Ga-PSMA-HBED-CC-PET/CT in patients with recurrent and high-risk prostate carcinoma. Eur J Nucl Med Mol Imaging. 2015. [Epub ahead of print].

52. Verburg FA et al. Extent of disease in recurrent prostate cancer determined by [Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. Eur J Nucl Med Mol Imaging. 2015. [Epub ahead of print].

53. Rowe SP et al. Comparison of PSMA-based 18F-DCFBC PET/CT to Conventional Imaging Modalities for Detection of Hormone-Sensitive and Castration-Resistant Metastatic Prostate Cancer. J Nucl Med. 2015. [Epub ahead of print].

54. Kularatne SA et al. Prostate-specific membrane antigen targeted imaging and therapy of prostate cancer using a PSMA inhibitor as a homing ligand. Mol Pharm. 2009;6(3):780-9.

55. Lapi SE et al. Assessment of an 18F-labeled phosphoramidate peptidomimetic as a new prostate-specific membrane antigen-targeted imaging agent for prostate cancer. J Nucl Med. 2009;50(12):2042-8.

56. Kularatne SA et al. Synthesis and biological analysis of prostate-specific membrane antigen-targeted anticancer prodrugs. J Med Chem. 2010;53(21): 7767-77.

57. Kabasakal L et al. Pre-therapeutic dosimetry of normal organs and tissues of (177)Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(13):1976-83.

58. Kasten BB et al. Targeting prostate cancer cells with PSMA inhibitor-guided gold nanoparticles. Bioorg Med Chem Lett. 2013;23(2):565-8.

59. Liu T et al. In vitro targeted photodynamic therapy with a pyropheophorbide--a conjugated inhibitor of prostate-specific membrane antigen. Prostate. 2009;69(6):585-94.

60. Sanna V et al. Development of polymeric microbubbles targeted to prostate-specific membrane antigen as prototype of novel ultrasound contrast agents. Mol Pharm. 2011;8(3):748-57.

TUBULAR ECTASIA OF THE RETE TESTIS: WHAT IS BEHIND IT?

***Ramón Rogel, Ana Avargues, Saturnino Luján, Jesús Andrés Betancourt, Enrique Broseta, Francisco Boronat**

Department of Urology, Hospital Universitari i Politècnic La Fe, Valencia, Spain
**Correspondence to ramonrogelberto@hotmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 22.02.16 **Accepted:** 15.03.16
Citation: EMJ Urol. 2016;4[1]:70–74.

ABSTRACT

Background: Tubular ectasia of the rete testis (TERT) is a dilatation of the seminiferous tubules of the mediastinum testis. It tends to be asymptomatic and usually constitutes an incidental finding of imaging studies. Scrotal ultrasound (SU) shows tubules with a cystic appearance, suggesting a number of possible diagnoses, including testicular tumours.
Objective: To review our experience and describe the clinical and ultrasound features.
Design: Retrospective descriptive review.
Setting: The images were obtained by SU on an ambulatory basis. SU was performed with the Pro Focus Ultrasound System (BK Medical®, Massachusetts, USA). The indications of the exploration, the SU findings, and the associated conditions were the variables analysed.
Participants: 460 SU studies performed in our hospital between 2010 and 2013. The subjects were men, with a median age of 66 years (range 47–78).
Outcome Measurements and Statistical Analysis: SPSS® version 20 (IBM, New York, USA) was used for the descriptive analysis of the data.
Results and Limitations: TERT was identified in 23 out of 460 SU studies performed. SU was indicated due to the presence of scrotal swelling in 7 patients (30%), an epididymal mass in 8 patients (35%), mild testicular pain in 6 patients (26%), and post-surgical control in 2 asymptomatic patients. Within the 23 patients, 10 (43.4%) were diagnosed with an epididymal cyst, 3 (13%) with chronic epididymitis, and 9 (39%) with a hydrocoele. With regard to associated conditions, 3 (13%) had undergone ipsilateral inguinal hernia repair, 3 (13%) had undergone ipsilateral hydrocoelectomy, and 1 (4%) had a history of contralateral testicular cancer. TERT was unilateral in all cases. No malignant degeneration of the lesions was observed in our series.
Conclusions: According to our experience, TERT is an incidental condition where detailed clinical history, adequate physical examination, and SU findings can lead to the diagnosis. Knowledge of this disease is therefore essential for urologists.
Patient summary: In this report we analyse the clinical features and the SU findings associated with TERT, a condition incidentally found in imaging studies of men in their 60s usually performed for other reasons.

Keywords: Tubular ectasia, scrotal ultrasound (SU), testicular cancer, differential diagnosis, rete testis, seminiferous tubules.

INTRODUCTION

Tubular ectasia of the rete testis (TERT) is a dilatation of the seminiferous tubules of the mediastinum testis. At ultrasound the tubules present with a cystic appearance.[1-3] Intratesticular cystic lesions include simple cysts, epidermoid cysts, TERT, intratesticular varicocoele, and abscesses. The true relevance of intratesticular lesions lies in their differential diagnosis (including testicular cancer), principally in young adults where they are most commonly diagnosed. An adequate diagnosis is therefore very important to avoid unnecessary imaging studies such as magnetic

resonance imaging (MRI) or orchidectomy.[1] An ultrasound diagnosis is not difficult to establish but a series of guidelines, which are commented upon in this study, must be taken into account.[3,4]

Most publications include a single case report or a series; for example, Burrus et al.,[1] which included 13 patients or Ortega et al.,[5] which included 19 patients. As far as we know, our series is one of the largest in the published literature. The objective is to review our experience in TERT diagnosis and management, and describe both clinical and ultrasound features.

METHODS

We conducted a retrospective study and reviewed 460 scrotal ultrasound (SU) studies performed in our hospital between January 2010 and November 2013. The images were obtained by SU in an outpatient setting; the patients were males attending the ultrasonography room. The indications for exploration ranged from testicular pain to swelling or suspected epididymal mass.

The variables analysed were age, presence of scrotal mass, swelling, pain, and trauma. SU findings categorised as 'normal images' included epididymal cysts, chronic epididymitis, hydrocoeles, testicular ischaemia, and haematocoeles. The associated conditions evaluated were cryptorchidism and inguinal hernia, and a history of orchidopexy, vasectomy, epididymectomy, previous hernia repair, hydrocoelectomy, as well as other medical conditions such as cirrhosis or end stage renal disease (ESRD) on haemodialysis or peritoneal dialysis.

SU studies were carried out using the Pro Focus Ultrasound System (BK Medical®, Massachusetts, USA) equipped with a small-part probe operating at a frequency of 8.0–12.0 MHz. Patients were received in the ultrasound exploration room and required no prior preparation of any kind. Exploration was performed in the supine decubitus position, with an estimated duration of 10–15 minutes. The lesions were located by obtaining a sagittal view of the testicle, with the mediastinum testis at the centre. TERT was diagnosed when cystic images were detected, mostly with a tubular or rosary-like morphology of variable number (usually >10) grouped at the upper pole of the testicle. Clear circumscribed circular images appeared to constitute independent cysts, though in most cases modification of the direction of the ultrasound beam showed that these elements correspond to normal tubules acquired in cross-section. Colour Doppler sonography revealed the absence of internal flow inside the cystic lesions, differentiating them from intratesticular varicocoele (Figure 1).

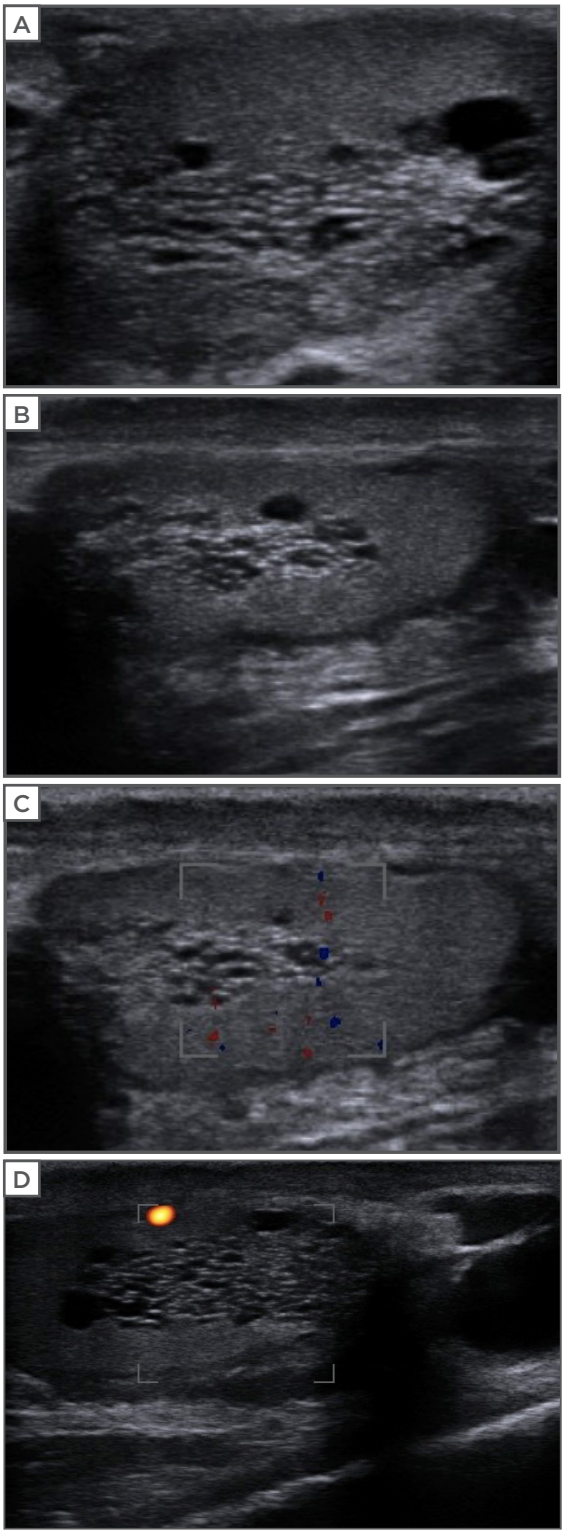


Figure 1: Ultrasound with and without added Doppler imaging showing tubular structures in the mediastinum testis lacking vascular flow.

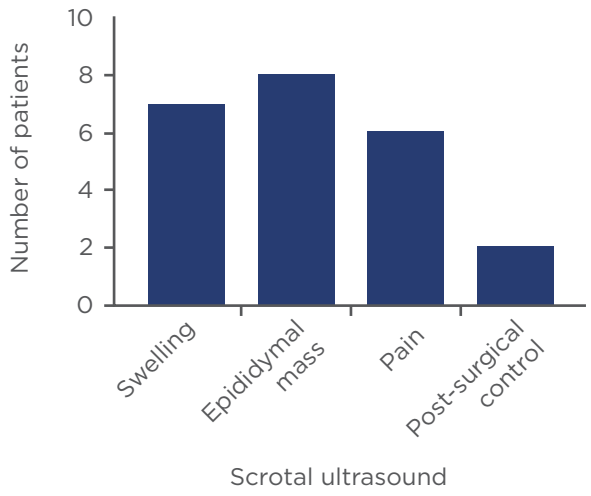


Figure 2: Scrotal ultrasound indication.

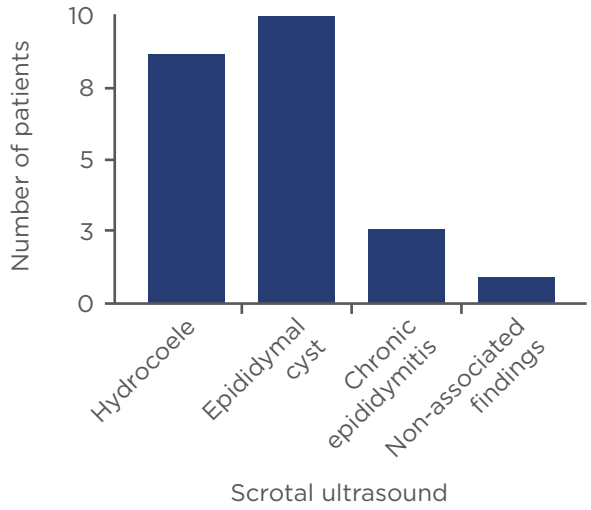


Figure 3: Scrotal ultrasound findings.

RESULTS

Among the 460 ultrasound studies performed, TERT was identified in 23 patients (5%) aged between 47 and 78 years (median 66 years) in the stated time period. TERT was found to affect up to two-thirds of the longitudinal diameter of the testicle in some cases. The mean size of the anechoic images was 0.7 mm.

In our series, ultrasound exploration was indicated due to scrotal swelling in 7 of the 23 patients (30%), epididymal masses in 8 cases (35%), mild testicular pain in 6 patients (26%), and post-surgical control in 2 asymptomatic patients (9%) (Figure 2). No indications were given after testicular trauma. Regardless of the indication, 10 of the 23 patients (43%) were diagnosed with epididymal cysts and 3 (13%) were diagnosed with chronic epididymitis, while 9 (39%) presented with a hydrocoele, and 1 (4%) had non-associated findings (Figure 3).

A number of associated conditions were observed; 3 patients (13%) had undergone ipsilateral inguinal hernia repair and 3 (13%) had undergone ipsilateral hydrocoelectomy, while 1 patient (4%) had a history of contralateral testicular cancer. This patient, a 54-year-old male, had been diagnosed with a Stage 1 testicular seminoma 20 years previous to the study.

None of the other factors that have previously been associated with this condition in the current literature, such as orchidopexy, vasectomy, epididymectomy, and other medical conditions such as cryptorchidism, cirrhosis, or ESRD with haemodialysis or peritoneal dialysis as a treatment were observed in this series of patients. Furthermore, none of our patients presented bilateral lesions.

DISCUSSION

The rete testis is formed by the confluence of the seminiferous tubules which fold to form a compact structure within the mediastinum testis and merge in the efferent ducts, which conform the epididymal head.[5] From an aetiological perspective, obliteration of the seminiferous tubules, due to either luminal obstruction or external compression, causes the formation of the cystic dilatations that characterise this condition. The tubules may contain spermatozoa and can be connected to the lumen of non-dilated ducts in cases of partial obstruction.

According to the existing literature, TERT is a condition that affects middle-aged men and its prevalence increases with age;[6] in our series, the youngest patient was 47 years old. Nevertheless, most diagnoses correspond to patients in the sixth decade of their life and onwards. From a clinical point of view, TERT tends to be asymptomatic at the time of diagnosis and often constitutes an incidental finding in imaging studies performed for other indications.

To date, a number of factors have been related to the disease, including epididymal alterations such as cysts, chronic epididymitis, or epididymectomy, as well as space-occupying lesions such as testicular tumours. Haematocoele has been described as a cause of extrinsic tubular compression. Other causes

are cryptorchidism and vasectomy. From a systemic point of view, cirrhosis has been described as a possible triggering factor, giving rise to hormonal alterations that can lead to ischaemia of organs such as the testes. Other systemic causal factors are haemodialysis or peritoneal dialysis secondary to the accumulation of calcium oxalate crystals within the tubular lumen.[2,6,7] Histological studies from autopsies in men who underwent haemodialysis or peritoneal dialysis showed epithelium columnar transformation with occasional papillary proliferations without finding evidence of atypia or mitoses. In our study, we also identified hydrocoele and inguinal hernia repair as possible causes, likely due to pressure exerted upon the testicular cord.

Despite malignant transformation of the rete testis being rare, some past literature has referred to it, always acknowledging the rarity of this degeneration.[8] Since the bulk of the evidence suggests that TERT is a condition with benign behaviour, a correct differential diagnosis is the most important aspect of the disease. In the presence of a cystic image in the mediastinum testis, it is important to know the features that allow us to distinguish between the different possible diagnoses. Intratesticular varicocoele has ultrasound characteristics that are very similar in terms of morphology and location to those of TERT. However, the two conditions can be clearly distinguished using Doppler ultrasound sonography, which reveals a slow vascular flow in cases of varicocoele, a finding that is absent in tubular ectasia. This flow is more obvious during a Valsalva manoeuvre or in the standing position. Intratesticular varicosities usually appear in patients with extratesticular varicocoele. In addition, a hypotrophic ipsilateral testis may be observed, which can manifest as testicular asymmetry.[9,10]

Another similar condition which simulates TERT is cystic dysplasia. Cystic dysplasia typically appears in the paediatric population, with a mean age of 5.8 years at presentation.[11] It was first described by Leissring and Oppenheimer.[12] When cystic dysplasia is detected, a radiologic evaluation of the upper urinary tract should be performed because its presentation is usually associated with other urological anomalies. Multiple treatment options have been proposed from orchiectomy to cyst excision. As the lesion is benign and malignant degeneration has never been reported, conservative management may be an option.[13]

Cysts of the tunica albuginea are small anechoic nodules generally located within the superficial testicular layers, and show no flow signal in Doppler exploration. Furthermore, these lesions are palpable at physical examination and are commonly discovered by the patient; they are usually described as a painless nodule <5 mm. Detection of these cysts may follow a haemorrhage, trauma, or infection of the cyst. Most cases require no subsequent treatment measures.[14]

Lastly, it is essential to distinguish TERT from testicular tumours, especially in cases where cystic formations are common, for example in patients presenting with testicular teratoma.[4] Age may offer distinguishing information, with testicular tumours affecting more young men than TERT. These patients usually consult for a hard testicular nodule or an increase in the diameter of a testis. A key ultrasound feature in these cases is increased blood flow around the testicular tumour cyst upon Doppler exploration. This usually corresponds to the proliferative state of tumour tissue surrounding a cyst. Cysts can present as multi-septum, heterogeneous, expansive lesions, and may be observed in the interpolar region of the testicle. Microlithiasis may also be observed inside or nearby the lesion.[15,16] In the event of diagnostic doubt following SU, serum β-human chorionic gonadotropin, α-fetoprotein, and lactate dehydrogenase testing should be performed, as well as a genital and pelvic MRI study. One patient in our series was previously affected by contralateral seminoma (20 years ago); the subsequent follow-up includes monitoring of serum tumour markers, SU, and chest X-rays performed on an annual basis. No malignant transformation of the lesions was observed in our series of cases and it is an uncommon condition in the reviewed literature.

None of our patients presented with bilateral lesions, probably due to having local and unilateral findings on SU and associated conditions, which are probable causes of TERT. No conditions with the potential to affect both testes, such as vasectomy or systemic diseases, were observed in our series. No treatment measures are required following the diagnosis, and no subsequent serial imaging controls are usually needed.[1,2,17]

CONCLUSION

TERT is a condition typically found in men >50 years of age. It tends to be an incidental

finding in the context of SU exploration performed for other reasons. Imaging appears very typical, though the differential diagnosis is comprised of a range of conditions that include testicular tumours with a cystic component as a worrying possibility. However, few cases of malignant transformation have been found in the reviewed literature. Consequently, follow-up or treatment is usually not necessary, provided a firm diagnosis has been established.

REFERENCES

1. Burrus JK et al. Cystic ectasia of the rete testis: clinical and radiographic features. J Urol. 2002;168(4 Pt 1):1436-8.

2. Nistal M et al. Cystic transformation of the rete testis. Am J Surg Pathol. 1996;20(10):1231-9.

3. Rouvière O et al. Tubular ectasia of the rete testis: a potential pitfall in scrotal imaging. Eur Radiol. 1999;9(9):1862-8.

4. Dogra VS et al. Benign intratesticular cystic lesions: US features. Radiographics. 2001;21 Suppl 1:S273-81.

5. Ortega Herrera R et al. Tubular ectasia of the rete testis: ultrasonography findings in 19 patients. Arch Esp Urol. 2000;53(5):455-9.

6. Stewart VR, Sidhu PS. The testis: the unusual, the rare and the bizarre. Clin Radiol. 2007;62(4):289-302.

7. Nair R et al. Tubular Ectasia of the Rete Testis: A Diagnostic Dilemma. Ann R Coll Surg Engl. 2008;90(7):W1-3.

8. Yang Z et al. Adenocarcinoma of the rete testis with widespread liver metastasis. Can Urol Assoc J. 2013; 7(9-10):E654-6.

9. MacLachlan LS et al. Intratesticular varicoceles: are they significant? J Pediatr Urol. 2013;9:851-5.

10. Bucci S et al. Intratesticular varicocele: evaluation using grey scale and color Doppler ultrasound. World J Urol. 2008; 26(1):87-9.

11. Eberli D et al. Cystic dysplasia of the testis: a very rare paediatric tumor of the testis. Urol Int. 2002;69(1):1-6.

12. Leissring JC, Oppenheimer RO. Cystic dysplasia of the testis: a unique congenital anomaly studied by microdissection. J Urol. 1973;110:362-3.

13. Mac New HG et al. Cystic dysplasia of the rete testis. J Pediatr Surg. 2008; 43(4):768-70.

14. Alvarez DM et al. Sonographic Spectrum of Tunica Albuginea Cyst. J Clin Imaging Sci. 2011;1:5.

15. Di Renzo D et al. Testicular teratoma, mimicking a simple testicular cyst, in an infant. Urology. 2013;82(3):701-3.

16. Epifanio M et al. Mature testicular teratoma in children: multifaceted tumors on ultrasound. Urology. 2014;83(1):195-7.

17. Pascual Mateo C et al. Cystic ectasia of the rete testis. Arch Esp Urol. 2006; 59(1):55-8.

SURGICAL MANAGEMENT OF POST-PROSTATECTOMY INCONTINENCE

Arthi Satyanarayan, Ryan Mooney, *Nirmish Singla

Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA
**Correspondence to nirmish.singla@phhs.org*

Disclosure: The authors have declared no conflicts of interest.
Received: 14.12.15 **Accepted:** 18.02.16
Citation: EMJ Urol. 2016;4[1]:75-80.

ABSTRACT

Post-prostatectomy incontinence (PPI) is a common and significant issue that can affect the quality of life in men who are undergoing treatment for prostate cancer. While some patients opt for conservative management of their incontinence, many elect to undergo surgical treatment as a result of the significant impact to quality of life. The most commonly employed surgical techniques to address PPI are placement of a male sling or artificial urinary sphincter (AUS). Currently, the AUS continues to serve as the gold standard for management, with robust data concerning longitudinal outcomes available. However, in recent years, the various methods to place the male sling have emerged as viable, less complex alternatives that avoid the need for pump manipulation. In the present review, we discuss these main surgical treatment modalities for PPI, and focus on the selection criteria that may influence appropriate operative stratification of PPI patients. Indeed, an individualised, comprehensive assessment of baseline urinary function, age, radiation, prior surgeries, functional status, and other comorbidities must be considered in the context of shared decision-making between the treatment provider and the patient in determining the optimal approach to managing PPI.

Keywords: Urinary incontinence, prostatectomy, male sling, artificial urinary sphincter (AUS).

INTRODUCTION

Stress urinary incontinence (SUI) refers to the involuntary leakage of urine due to increases in abdominal pressure. In men, SUI is most commonly seen following radical prostatectomy. Sphincter insufficiency has been found to be present in up to 88% of patients and is thought to be the primary underlying aetiology of post-prostatectomy incontinence (PPI), though frequently detrusor instability or impaired contractility are present.[1] While urinary incontinence is almost universally evident immediately following prostatectomy, the severity and degree of recovery are variable. Reported rates of incontinence following radical prostatectomy range from 5–72%,[2] though this is partly due to the absence of a strict definition for PPI. With the advent of minimally invasive technologies, robotic approaches to performing prostatectomy have become widely popularised; nonetheless PPI remains an issue, with a reported incidence of 4–31% in robotic cases, versus 7–40% reported for open cases.[3] Others have reported PPI rates of <10% with improvement over the first 24 months following surgery.[4] Depending on the degree of leakage, PPI can have a significant impact on the quality of life in patients who have already undergone treatment for prostate cancer. Approximately half of patients seek some management for PPI,[5] and 6–9% elect to undergo surgical treatment.[5-12] The most commonly employed surgical techniques to address PPI include placement of a male sling or an artificial urinary sphincter (AUS). Presently, the AUS serves as the gold standard for management,[13] with several studies demonstrating favourable long-term outcomes. Of the sphincters available the AMS 800 has been utilised most in the last 40 years. Other options include the ZSI 375 AUS from Switzerland, which consists of a cuff and pump only, and the inflatable periurethral constrictor.[3] AUS success rates have been reported as between 54% and 91% in contemporary series or higher, dependent on the definition of success used and the baseline patient characteristics.[14]

More recently, the male sling has emerged as a viable, less complex alternative, which avoids the need for pump manipulation and is particularly suited for patients with mild-to-moderate PPI severity.[14,15] There are a variety of male sling options available, including the bone anchored sling (Invance™), the retrourethral transobturator sling (Advance®), and the adjustable retropubic sling (Argus®).[16] In the present review, we discuss the surgical treatment modalities available for PPI, with a particular focus on the selection criteria that may influence appropriate operative stratification of patients with PPI.

SURGICAL TREATMENT OPTIONS FOR POST-PROSTATECTOMY INCONTINENCE

Artificial Urinary Sphincter

The modern AUS design was initially introduced in the 1970s.[17,18] The continence mechanism of the AUS relies on three components: a cuff that circumferentially occludes the urethra, a pressure regulating balloon (PRB) that may be placed in either retropubic space or an ectopic location,[19] and a pump-control mechanism placed in the scrotum. The pump acts as a user interface, whereby the patient can be in control of his continence.

Some variation exists in the surgical approach to AUS implantation. At our institution, the surgery typically begins with a midline perineal incision that continues to the bulbospongiosus muscle. The muscle is split and the urethra is dissected circumferentially at its thickest aspect, the proximal bulbar urethra, as it passes through the urogenital diaphragm. The circumference of the urethra is measured, and a cuff of approximately the same size is secured around the urethra. Cuff sizes can vary and are traditionally ≥4 cm in size; in 2009, however, a 3.5 cm cuff was introduced, and recent data from our institution have shown promising results with this smaller cuff.[20,21] Using a separate incision in the upper scrotum, a PRB and pump are placed. The retropubic space has traditionally served as the standard location for PRB implantation; however, as this approach requires that the transversalis fascia is punctured and due to the potential complications related to the surrounding blood vessels and organs, ectopic PRB placements have been suggested with promising results.[19,22] At our institution, a high sub-muscular approach is preferred in which the PRB is tunnelled beneath the rectus abdominis muscle using a Foerster lung grasping clamp, without entering the peritoneum.[19,22] The pump can then be placed into the subdartos space in the scrotum through the scrotal incision. Finally, the tubing connections are connected, and the device is cycled and locked. A urethral catheter is retained overnight and removed on Day 1 postoperatively.

Male Slings

The advent of male slings has greatly diversified the available treatment options. Various designs have been described, including both adjustable and non-adjustable types.[15,23] The bone anchor sling is a polypropylene mesh that is affixed to the bony pelvis, thus avoiding the retropubic space, which may contain scar tissue from the patient's prior prostatectomy. Slings made of organic material may also be used, but they have higher incidences of degrading. Studies have indicated that the bone anchor sling causes urethral compression, most likely by increasing transmission of intra-abdominal pressure to the bulbar urethra.[15] Success with the bone anchor sling has been reported to range from 40–88%.[16]

The transobturator male sling was approved in the United States by the Food and Drug Administration (FDA) in 2006, based on encouraging results of transobturator tape in women. The technique entails placement of the sling through the obturator foramen, which is further described in a study by Rehder and Gozzi.[24] Early results demonstrated a cure rate of 52%, an improvement rate of 38%, and a significant decrease in the median incontinence pad usage.[25] The surgery has been reported to be an overall success in 76–91% of cases, though the transobturator sling is not as efficacious in patients with prior radiation compared with bone anchor slings. Placement of a transobturator sling does not result in urodynamic obstruction.[16]

There are a large variety of adjustable slings available. The adjustable retropubic sling is positioned in the retropubic space and secured to the abdominal fascia with ribbed silicone struts and washers, which are designed to provide the ability for sling adjustment accordingly.[16] Newer therapies and variations are currently underway, and the outcome data of patients who elect to receive these treatment modalities for their PPI are still forthcoming. Success rates in patients with adjustable slings have been more consistently reported in 72–79% of patients; however, an increasing number of patients have reported rates of mesh erosion (3–13%).[16] Some of these

newer-generation adjustable slings may help extend the patient candidacy of male slings.[26]

PATIENT STRATIFICATION AND CONSIDERATIONS

The decision to pursue AUS versus sling in patients relies on a range of factors, and we currently lack a standardised algorithm for deciding which option would better serve a patient's needs. While slings can be effective for the management of mild-to-moderate SUI (Grade B evidence), severe SUI is better managed with AUS (Grade C evidence).[27,28] However, distinguishing among incontinence severities is based on a subjective evaluation involving some combination of history, physical examination, usage of incontinence pads per day (PPD), pad weights, cystoscopy, and urodynamics.

Some of our objective measures may add only limited value in stratifying patients opting for surgical management of PPI.[29,30] Urodynamic evaluation in particular has been shown to correlate poorly with anti-incontinence surgical outcomes.[29-31] The role of abdominal leak point pressure (ALPP) in predicting the degree of urinary incontinence following prostatectomy is also dubious as studies have failed to show any correlation of ALPP with severity of sphincter damage and SUI.[30] Thiel et al.[29] evaluated a comprehensive series of clinical and urodynamic parameters (detrusor over-activity, low first sensation, low bladder compliance, and low bladder capacity) for men with PPI, but none were predictive of successful AUS outcomes.[29] Furthermore, none of these parameters were correlated with patient-reported usage of PPD. Taken together, these results mirror those of the multicentre, randomised, non-inferiority Value of Urodynamic Evaluation (VALUE) trial, which found that urodynamic testing in a large cohort of women with uncomplicated, demonstrable SUI did not affect the outcome of surgical intervention.[31]

Currently available studies regarding AUS and sling outcomes are retrospective in nature, and presently there is a lack of prospective, randomised trials comparing these two modalities. As such, an individualised, comprehensive assessment of baseline urinary function, age, radiation, prior surgeries, functional status, and other comorbidities must be considered in the context of shared decision-making between the treatment provider and patient in determining the optimal approach to managing PPI.

AUS remains the gold standard for surgical treatment of PPI based on the robust long-term outcomes data that is available.[13] AUS may be used either as a primary surgical treatment for PPI or as a secondary surgical intervention following failure of a prior sling or AUS. Long-term data demonstrate near complete resolution of PPI (0–1 PPD) in 59–89% of patients with variable length of follow-up.[32-34] A recent review of management of PPI indicated that patients who received AUS represented the highest percentage of patients successfully treated for continence.[3]

Persistent incontinence despite AUS is a common reason for surgical revision and may be corrected with urethral cuff downsizing, repositioning, or tandem cuff placement. Tandem cuff placement is reported to be superior to cuff repositioning in treating persistent urinary incontinence, while urethral cuff downsizing may be associated with an increased rate of mechanical failure.[35] Double or tandem cuff implantation is not recommended as an initial operative treatment, as it is shown to increase rates of explantation, revision, and infection.[36]

Long-term rates of AUS revision have been reported to be approximately 25%, owing to complications such as infection, erosion, mechanical failure, or urethral atrophy.[37] When considering this data, AUS may conceivably be a less desirable option in patients with mild-to-moderate PPI. Unlike the AUS, which chronically compresses the urethra circumferentially and often predisposes patients to urethral atrophy or cuff erosion, the male sling compresses only the ventral aspect of the bulbar urethra, leaving dorsal and lateral spongiosal blood flow intact. In a recent study by Kumar et al.,[38] which compared patient preference (sling versus AUS), only 75% of patients chose AUS when recommended by a urologist. The remaining 25% chose to undergo a sling procedure against the advice of the surgeon. As indicated in the study, patients who chose to pursue a sling procedure against the advice of the urologist reportedly did so to avoid the need to manually operate the AUS device. Conversely, all patients chose a male sling when recommended by the urologist. When given the option between AUS and male sling, 92% of patients chose the sling.[38]

Although the follow-up duration tends to be shorter in the male sling literature than in the AUS literature, the male sling appears to be a reasonable alternative to AUS as a first-line treatment in appropriately selected patients with

mild-to-moderate PPI. The perineal dissection is similar to that in AUS placement, though without the need for a second counter-incision and the added risk of complications from a multi-component device. The most common complication associated with slings is acute urinary retention, which is reported in up to 24% of patients.[14] Infection remains a risk, as with the implantation of any foreign body, though studies appear to demonstrate a higher risk of this complication in adjustable male slings than in nonadjustable slings.[14] A recent comparison between transobturator sling versus AUS as primary surgical treatment reveals no significant difference in postoperative continence (0–1 PPD), improvement, patient satisfaction, or complication rates between the two.[39] The authors noted that the complication severity was greater in the AUS patients. The mean follow-up for the AUS group was 43 months, compared with only 24 months for patients receiving slings. In another study by Lim et al.[40] in 33 patients with mild PPI and similar length of follow-up, there was no statistical difference in success or complication rates between patients who received adjustable male slings and those who underwent AUS implantation.

Failure of Prior Incontinence Surgery

Certain risk factors have been identified that may complicate PPI surgery, or increase risk of postoperative complications. Patients with these factors deserve special consideration and ought to be counselled heavily regarding their options and the available data. One such population is those who have undergone prior sling or AUS and have either recurrent or persistent incontinence. Ajay et al.[41] recently reported a drastically higher success rate after AUS (94%) than repeat transobturator sling placement (45%) following previous sling failure. Similarly, in another study by Tuygun et al.,[42] AUS demonstrated a higher cure rate (75%) than adjustable bulbourethral male sling placement (25%) following previous AUS erosion (mean follow-up, 10 and 22 months, respectively). While the success rate of male slings tends to be reduced in patients with failed prior slings,[16,43] AUS placement following sling failure has demonstrated similar outcomes and complication rates when compared with primary AUS as initial treatment of PPI.[44] Hence, in the setting of failed prior incontinence surgery, AUS is generally preferred over sling placement.

Prior Radiation

As multimodal approaches to managing prostate cancer continue to emerge and be refined, the number of patients seeking management of PPI with a prior history of radiotherapy is increasing. Radiation can cause progressive tissue changes including obliterative endarteritis and tissue atrophy.[45,46] This often makes surgical dissection more difficult and compromises postoperative healing, thereby predisposing patients to increased rates of complication and failure following PPI surgery. Radiation has been identified as an independent predictor for cuff erosion following AUS.[47] A recent meta-analysis revealed increased rates of persistent urinary incontinence, erosions, and device infections in patients managed with AUS for PPI after radical prostatectomy and external beam radiation therapy, compared with radical prostatectomy alone.[48] Male slings also tend to have higher failure rates following prior radiation.[16,43] While comparative studies of sling versus AUS in the post-irradiation setting currently appear to be lacking, we are generally very cautious in offering slings to patients with prior radiation given the concerns of a higher likelihood of failure. AUS is preferred in this setting, though it is important that these patients understand the greater risk of complications and failure of any form of surgical intervention. Kim et al.[14] noted that patients with a history of pelvic irradiation are more likely to require readjustment of their slings, suggesting perhaps that such patients should be counselled on receiving an adjustable sling over a non-adjustable type, if a sling is ultimately chosen despite extensive counselling and discussion of options.

CONCLUSION

PPI can significantly impact the quality of life of men following treatment for prostate cancer. Surgical management of PPI presently entails two widely employed approaches, namely AUS, which is currently considered the gold standard, and the male sling, which was developed more recently and continues to gain favourability in selected cases. The decision to pursue an AUS or sling relies on a range of factors, and we currently lack a standardised algorithm to surgically stratify patients. There is a growing need for prospective data comparing the efficacy of these modalities in various settings, and such data may help direct clinicians in counselling PPI patients appropriately.

Nonetheless, at present an individualised, comprehensive assessment of baseline urinary function, age, radiation, prior surgeries, functional status, and other comorbidities must be considered in the context of shared decision-making between treatment provider and patient in determining the optimal approach to managing PPI.

REFERENCES

1. Groutz A et al. The pathophysiology of post-radical prostatectomy incontinence: a clinical and video urodynamic study. J Urol. 2000;163(6):1767-70.

2. Boorjian SA et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. Eur Urol. 2012; 61(4):664-75.

3. Crivellaro S et al. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. Neurourol Urodyn. 2015. [Epub ahead of print].

4. Tewari AK et al. Functional outcomes following robotic prostatectomy using athermal, traction free risk-stratified grades of nerve sparing. World J Urol. 2013;31(3):471-80.

5. Penson DF et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. J Urol. 2008; 179(5 Suppl):S40-4.

6. Anastasiadis AG et al. Radical retropubic versus laparoscopic prostatectomy: a prospective comparison of functional outcome. Urology. 2003;62(2):292-7.

7. Begg CB et al. Variations in morbidity after radical prostatectomy. N Engl J Med. 2002;346(15):1138-44.

8. Jacobsen NE et al. Open versus laparoscopic radical prostatectomy: a prospective comparison of postoperative urinary incontinence rates. J Urol. 2007; 177(2):615-9.

9. Sacco E et al. Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up. BJU Int. 2006;97(6):1234-41.

10. Singla AK. Male incontinence: Pathophysiology and management. Indian J Urol. 2007;23(2):174-9.

11. Stanford JL et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA. 2000;283(3):354-60.

12. Steineck G et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med. 2002;347(11):790-6.

13. Shabbir M. Post-prostatectomy incontinence in the irradiated patient: more than just a drop in the ocean. BJU Int. 2015;116(4):502-3.

14. Kim SW et al. Male Readjustable Sling (MRS) System for Post-prostatectomy Incontinence: Experiences of Two Centers. Urology. 2015. [Epub ahead of print].

15. Singla N, Singla AK. Post-prostatectomy incontinence: Etiology, evaluation, and management. Turk J Urol. 2014;40(1):1-8.

16. Welk BK, Herschorn S. The male sling for post-prostatectomy urinary incontinence: a review of contemporary sling designs and outcomes. BJU Int. 2012;109(3):328-44.

17. Rosen M. A simple artificial implantable sphincter. Br J Urol. 1976;48(7):675-80.

18. Scott FB. The artificial urinary sphincter: review and progress. Med Instrum. 1988;22(4):174-81.

19. Singla N et al. Does Pressure Regulating Balloon Location Make a Difference in Functional Outcomes of Artificial Urinary Sphincter? J Urol. 2015;194(1):202-6.

20. Simhan J et al. 3.5 cm artificial urinary sphincter cuff erosion occurs predominantly in irradiated patients. J Urol. 2015;193(2):593-7.

21. Hudak SJ, Morey AF. Impact of 3.5 cm artificial urinary sphincter cuff on primary and revision surgery for male stress urinary incontinence. J Urol. 2011;186(5):1962-6.

22. Morey AF et al. High submuscular placement of urologic prosthetic balloons and reservoirs via transscrotal approach. J Sex Med. 2013;10(2):603-10.

23. Chung E et al. Adjustable versus non-adjustable male sling for post-prostatectomy urinary incontinence: A prospective clinical trial comparing patient choice, clinical outcomes and satisfaction rate with a minimum follow up of 24 months. Neurourol Urodyn. 2015. [Epub ahead of print].

24. Rehder P, Gozzi C. Transobturator sling suspension for male urinary incontinence including post-radical prostatectomy. Eur Urol. 2007;52(3):860-6.

25. Gozzi C et al. Early results of transobturator sling suspension for male urinary incontinence following radical prostatectomy. Eur Urol. 2008;54(4): 960-1.

26. Bauer RM et al. AdVanceXP male sling: 2-year results of a multicentre study. World J Urol. 2015. [Epub ahead of print].

27. Lucas MG et al. EAU guidelines on surgical treatment of urinary incontinence. Actas Urol Esp. 2013;37(8):459-72.

28. Samli M et al. Artificial urinary sphincter versus bone anchored male sling for post-radical prostatectomy urinary incontinence. Eur Urol. 2005;4(3):143.

29. Thiel DD et al. Do clinical or urodynamic parameters predict artificial urinary sphincter outcome in post-radical prostatectomy incontinence? Urology. 2007;69(2):315-9.

30. Twiss C et al. Correlation of abdominal leak point pressure with objective incontinence severity in men with post-radical prostatectomy stress incontinence. Neurourol Urodyn. 2005;24(3):207-10.

31. Nager CW et al.; Urinary Incontinence Treatment Network. A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med. 2012;366(21):1987-97.

32. Gousse AE et al. Artificial urinary sphincter for post-radical prostatectomy urinary incontinence: long-term subjective results. J Urol. 2001;166(5):1755-8.

33. Kim SP et al. Long-term durability and functional outcomes among patients with artificial urinary sphincters: a 10-year retrospective review from the University of Michigan. J Urol. 2008;179(5):1912-6.

34. Montague DK. Long-term continence and patient satisfaction after artificial sphincter implantation for urinary incontinence after prostatectomy. J Urol. 2001;166(2):547-9.

35. Eswara JR et al. Revision Techniques After Artificial Urinary Sphincter Failure in Men: Results From a Multicenter Study. Urology. 2015;86(1):176-80.

36. Kretschmer A et al. Risk factors for artificial urinary sphincter failure. World J Urol. 2015. [Epub ahead of print].

37. Lai HH et al. 13 years of experience with artificial urinary sphincter implantation at Baylor College of Medicine. J Urol. 2007;173(3):1021-5.

38. Kumar A et al. Artificial urinary sphincter versus male sling for post-prostatectomy incontinence--what do patients choose? J Urol. 2009;181(3): 1231-5.

39. Hoy NY, Rourke KF. Stemming the tide of mild to moderate post-prostatectomy incontinence: A retrospective comparison of transobturator male slings and the artificial urinary sphincter. Can Urol Assoc J. 2014;8(7-8):273-7.

40. Lim B et al. Comparing Argus sling and artificial urinary sphincter in patients with moderate post-prostatectomy incontinence. J Exerc Rehabil. 2014;10(5): 337-42.

41. Ajay D et al. The Artificial Urinary Sphincter is Superior to a Secondary Transobturator Male Sling in Cases of a Primary Sling Failure. J Urol. 2015; 194(4):1038-42.

42. Tuygun C et al. Comparison of outcomes for adjustable bulbourethral male sling and artificial urinary sphincter after previous artificial urinary sphincter erosion. Urology. 2009;73(6):1363-7.

43. Athanasopoulos A et al. Efficacy of the InVance male sling in treating stress urinary incontinence: a three-year experience from a single centre. Urol Int. 2010;85(4):436-42.

44. Lentz AC et al. Outcomes following artificial sphincter implantation after prior unsuccessful male sling. J Urol. 2012;187(6):2149-53.

45. Fajardo LF. The pathology of ionizing radiation as defined by morphologic patterns. Acta Oncol. 2005;44(1):13-22.

46. Turina M et al. Frequency and surgical management of chronic complications related to pelvic radiation. Arch Surg. 2008;143(1):46-52.

47. Raj GV et al. Outcomes following erosions of the artificial urinary sphincter. J Urol. 2006;175(6):2186-90.

48. Bates AS et al. Complications following artificial urinary sphincter placement after radical prostatectomy and radiotherapy: a meta-analysis. BJU Int. 2015;116(4):623-33.

EMJ EUROPEAN MEDICAL JOURNAL

EUROPEAN MEDICAL JOURNAL

provides influential articles, presentations of up-to-date scientific research and clinical practice, and in-depth reviews of international medical congresses.

Coming Soon

Please click **here** to:

- subscribe and receive the latest publications, newsletters & updates from **EMJ**
- view each edition in convenient eBook format; desktop, tablet & smartphone compatible

Follow us:

www.emjreviews.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

RENAL METASTASIS OF A MALIGNANT MYOPERICYTOMA: A CASE REPORT AND REVIEW OF LITERATURE

***Jeroen Van Besien,[1] Pieter Uvin,[1] Caroline Van den Broecke,[2] David Creytens,[3] Luc Merckx[1]**

1. Department of Urology, AZ Sint Lucas, Ghent, Belgium
2. Department of Pathology, AZ Sint Lucas, Ghent, Belgium
3. Department of Pathology, Ghent University Hospital, Ghent, Belgium
**Correspondence to jeroen.vanbesien@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 03.11.15 **Accepted:** 02.02.16
Citation: EMJ Urol. 2016;4[1]:82-87.

ABSTRACT

Myopericytoma is a rare tumour arising from myopericytes. Myopericytes are transitional cells between pericytes, which are perivascular cells adjacent to capillaries, and vascular smooth muscle cells. We report a case of cutaneous myopericytoma metastasising to the right kidney. It represents one of the few cases of malignant behaviour in myopericytoma, and is the first report of a myopericytoma metastasising to the urinary tract. This case suggests that the traditional view that urinary myopericytoma are benign lesions needs to be updated.

Keywords: Myopericytoma, malignant, renal.

INTRODUCTION

Myopericytoma is a rare tumour that arises from myopericytes. Myopericytes are transitional cells between pericytes, which are perivascular cells adjacent to capillaries and vascular smooth muscle cells. The term myopericytes was first used by Dictor et al.[1] in 1992 to describe a subset of myofibroblasts, and a few years later, the term myopericytoma was proposed by Requena et al.[2] The immunohistochemical characteristics were described by Granter et al.[3] in 1998.[2] Histologically, these tumours are characterised by concentric perivascular proliferation of spindle cells. Myopericytomas form a morphological spectrum of tumours with infantile haemangiomyopericytoma, solitary myofibroma, myofibromatosis, and myopericytoma; all of which show differentiation towards perivascular myoid cells or pericytes. In 2002, the World Health Organization (WHO) categorised these tumours under the group 'pericytic/perivascular tumours'.[4]

We report a case of cutaneous myopericytoma metastasising to the right kidney; this represents one of the few cases of a malignant behaviour in a myopericytoma, and the first case of a myopericytoma further metastasising to the urinary tract.

CASE REPORT

In November 2012, a 47-year-old woman consulted her dermatologist about a skin lesion in the upper middle quadrant of the right breast. The lesion was only slightly elevated and not well demarcated, with a purple angiomatous aspect. As the skin lesion was rapidly growing and presented an aesthetic problem, the woman was referred to a plastic surgeon for excision.

The lesion and a part of the underlying subcutis were removed with a minimal, lesion-free resection margin in December 2012. Microscopic examination showed a myopericytoma with atypical morphological features. Due to the presence of a high mitotic index (14/10 high power fields) and the presence of satellite nodules in the subcutaneous tissue, as well as uncertainty of the biological behaviour of the lesion, a broad resection was

performed. The section margins were tumour free and no additional staging was performed.

In 2014, the patient consulted a second plastic surgeon for aesthetic correction of the postoperative scar and palpation of a new mass underneath this scar. Clinical examination showed a hard, well-circumscribed mass in the right upper quadrant of the right breast. Clinically, the tumour was not adherent to the skin but possibly adherent to the underlying pectoralis muscle. A very broad resection of the lesion was performed with stripping of a pectoralis muscle patch. Anatomopathological results revealed necrotic material, which was impossible to differentiate, surrounded by an inflammatory reaction. Resection margins were free of tumour and no additional staging was performed.

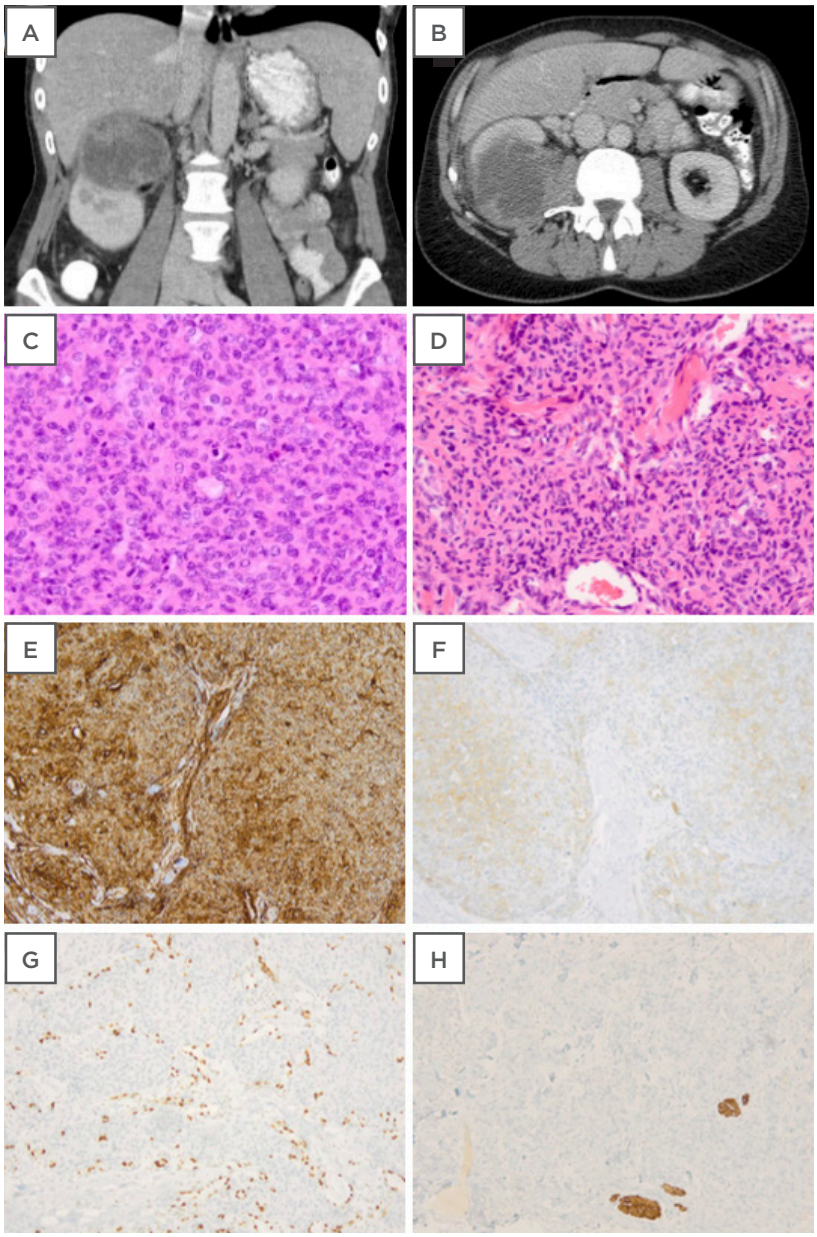


Figure 1: A,B) Computed tomography scan showing a malignant solid renal tumour of the kidney with irregular contrast captation. C) Haematoxylin and eosin staining of the kidney lesion showing a highly cellular tumour (100x). D) Hematoxylin and eosin staining of the original skin lesion showing morphology comparable to the kidney lesion. E) Immunohistochemical expression of CD34 in the original skin lesion. F) Focal immunohistochemical expression of alpha smooth muscle actin in the original skin lesion. G) Negative desmin control with internal positive control of arrector pili muscles in the original skin lesion. H) Negative ETS-related gene control of the original skin lesion with colouring of the tumour vasculature.

Table 1: Myopericytoma of the urinary tract.

Author and publication year	Age (years)/ Sex	Location	Size (cm)	Symptoms	Treatment	ANRM Outcome (Month)
Lau et al. 2010[7]	59/F	Left kidney	3.5	Incidental finding	Partial nephrectomy	8
Dhingra et al. 2012[8]	40/F	Left kidney	3.8	Left flank pain and frequency	Partial nephrectomy	24
Zhao et al. 2014[9]	59/F	Left kidney	3.5	Incidental finding	Radical nephrectomy	14
	52/F	Urinary bladder	6	Frequency and dysuria	Partial cystectomy	39
Zhang et al. 2014[20]	39/M	Left kidney	18	Painless mass left abdomen	Radical nephrectomy + LD	20
Li et al. 2015[11]	56/F	Right kidney	1.8	Pain on the right side of the abdomen	Partial nephrectomy	66
	33/M	Left kidney	4.5	Incidental finding	Radical nephrectomy	64
	46/M	Left kidney	7.3	Incidental finding	Radical nephrectomy	46
	70/M	Left kidney	4.8	Incidental finding	Radical nephrectomy	16
	69/M	Right kidney	4.2	Incidental finding	Radical nephrectomy	14
	59/M	Left kidney	3.6	Incidental finding	Radical nephrectomy	26

F: female; M: male; LD: lymph node dissection; ANRM: alive with no evidence of recurrent or metastatic disease.

In July 2015, the patient was referred to the department of internal medicine by her family doctor with weight loss of 8 kg, persistent fatigue, and pain in the right hypochondriac region. There were no urinary symptoms. Clinical examination revealed tenderness in the right hypochondriac region, and ultrasonography showed a mass on the upper pole of the right kidney. A computed tomography (CT) scan of the abdomen revealed a voluminous tumour of 8.2 cm in the upper pole of the right kidney. The tumour showed irregular contrast captation and was assessed as a malignant solid renal tumour, presumably renal cell carcinoma. No pathologically enlarged retroperitoneal nodes were seen (Figure 1A and 1B). A CT image of the thorax showed no abnormalities. A radical right nephrectomy was performed with an uncomplicated postoperative course.

Pathologic examination, however, showed no renal cell carcinoma, but a high-grade sarcomatous lesion. The tumour cells were polygonal or spindle shaped, with areas of necrosis and numerous mitoses. The cells were arranged in short fascicles, sometimes with a hemangiopericytoma-like pattern (Figure 1C). The kidney lesion was compared with the original skin tumour and showed similar morphology upon haematoxylin and eosin staining (Figure 1D), and immunohistochemistry (Figure 1E–H).

Immunohistochemical analysis revealed expression of CD34 (Dako Clone QBEnd 10) (Figure 1E), and only focal expression of myogenic markers such as smooth muscle actin (Dako Clone 1A4) (Figure 1F) and calponin (Dako Clone CALP). The tumour was negative for desmin (Dako Clone D33) (Figure 1G) and the *ETS-related gene* (Dako Clone EP111) (Figure 1H). These findings are compatible with a high-grade sarcoma with myopericytic differentiation. Both tumours showed a high mitotic index. The initial skin tumour showed low-grade cytonuclear atypia, while the kidney tumour showed a high grade of atypia.

Next generation sequencing was performed on the kidney lesion but no *BRAF* mutation was present.[5] Resection margins were free of tumour and no adjuvant therapy was given. A positron emission tomography (PET) CT conducted after 3 months (October 2015) showed no evidence of disseminated disease so far.

DISCUSSION

A myopericytoma is a rare tumour mostly arising in skin or superficial soft tissues. The largest case

series of 54 patients was described by Mentzel et al.[5] in 2006. In their series, 26 cases occurred in the lower extremities, 16 in the upper extremities, 4 in the head and neck region, and 2 in the trunk.[5] The presence of myopericytoma in visceral organs is rare, although occasional cases have been described in the thorax, lungs, heart, gastrointestinal tract, brain, and urinary tract.[6] Myopericytomas may have a tendency to recur locally, but most are benign tumours with an excellent prognosis.

Our case report of a myopericytoma is exceptional because of its location, namely the urinary tract. A search of English literature using the Medline database via PUBMED revealed 11 other cases of urinary myopericytoma (Table 1).[7-11] Within this literature, all but one of these tumours occurred in the kidney; in one case the urinary bladder was affected. The majority of the tumours were small, with a mean diameter of 5.5 cm and a median diameter of 4.5 cm. Commonly, the lesions were incidental findings on imaging studies; though, in one case of a large mass of the left kidney, the lesion was found during clinical examination. Frequency, dysuria, or abdominal/flank pain have also been described. The age of patients diagnosed with urinary myopericytoma was variable, with the youngest patient being a 33-year-old male. None of these patients developed any evidence of recurrent or metastatic disease after surgical removal of the lesion (mean follow-up: 30 months).

Our case concerned a malignant myopericytoma. In contrast to the typical myopericytoma, this tumour has atypical features such as a high mitotic index, nuclear pleomorphism, necrosis, and high cellularity. In 2002, McMenamin and Fletcher[12] named these tumours malignant myopericytomas. Incidence of these tumours is extremely rare; to our knowledge, only eight cases have been described in the literature (Table 2).[5,12-14] The majority of these tumours appear to be located superficially, with only the skin and subcutaneous tissue affected. To date, only single cases of malignant mediastinal myopericytoma, malignant left atrial myopericytoma, and malignant intradural myopericytoma have been described.[12-14]

Table 2: Cases of malignant myopericytoma in the literature.

Study	Age (years)/ sex	Location	Size (mm)	Symptoms	Treatment	ANRM Outcome
McMenamin et al.[12] (2002)	80/F	Left side of neck	20	Painless rapidly growing mass	Marginal excision	Alive with liver metastases at 14 months
	46/M	Left thigh	130	Painful deep-seated IM mass	Wide local excision + EBRT	Death at 7 months with liver, brain, and heart metastases at 6 months
	19/F	Heel of right foot	40	Painful mass	Below knee amputation	Death within 1 year
	81/M	Left arm	15	Painless mass	Wide local excision	ANRM at 18 months
	67/M	Mediastinal mass and skin nodule	100 and 8	SVC obstructive symptoms	Excision of skin nodule	Death within 1 month with subcutaneous and skin metastases
Mentzel et al.[5] (2006)	61/M	Lower leg	NS	Painless subcutaneous mass	Wide local excision	ANRM. Period not specified.
Mainville et al.[13] (2015)	52/M	Left atrium	NS	Blackening of the LFV	Excision atrial mass	Alive with brain, skeletal, and liver metastasis at 8 months
Holling et al.[14] (2015)	38/M	Intradural L5/S1	NS	Pain right dorsal calf	Excision atrial mass	ANRM at 18 months
Van Besien et al. (2016)	47/F	Right breast and right kidney	4.2 and 82	Weight loss, fatigue, flank pain	Excision of skin nodule and kidney metastasis	ANRM at 3 months

F: female; M: male; L5: lumbar 5; S1: sacral 1; NS: not specified; IM: intermuscular; SVC: superior vena cava; LFV: left field of vision; EBRT: external beam radiation therapy; ANRM: alive with no evidence of recurrent or metastatic disease.

Although metastasis of a malignant myopericytoma to the liver, brain, skeletal system, and heart have previously been described, this report represents the first described case of a metastasis of a malignant myopericytoma in the urinary tract.

Benign myopericytomas are diagnosed by excisional biopsy. The pathological result is often a surprise to the treating physician due to the rarity of these tumours. Diagnosis is further confirmed by immunohistochemical analysis as myopericytes are immunoreactive for smooth muscle actin and CD34, but rarely for desmin.[6] However, no data exist for the follow-up or staging of these tumours. In cases of superficial myopericytoma with classic histological features, complete excision is curative. When these tumours are located in visceral organs additional staging is often performed by imaging studies. However, the prognosis of benign myopericytomas tends to be good.

Malignant myopericytomas may present as a primary metastatic disease, or may rapidly metastasise as described above. Broad excision of these lesions with high mitotic index is the treatment of choice. Despite broad resection, the prognosis of a malignant myopericytoma remains unclear. Out of the five cases described by McMenamin and Fletcher,[12] three patients died within the first year. The two surviving patients showed varying status; one developed liver metastases during the follow-up period of 14 months, and the other survived with no evidence of recurrent or metastatic disease after surgical removal of the lesion. In another report from 2006, a subcutaneous malignant myopericytoma of the lower leg was treated by resection without any evidence of recurrent or metastatic disease. The follow-up period was undefined.[5] Two recent papers have reported cases of malignant myopericytomas, one in the left atrium and one in the dura mater. Of these papers, the former reported metastases to the brain, skeletal system, and liver after 8 months, while the latter paper reported no evidence of recurrent or metastatic disease after 18 months.[13,14]

Until recently, there were no data available about the value of adjuvant therapy in preventing local recurrence or metastases of this disease. One case report described wide excision of a deep-seated, intermuscular malignant myopericytoma followed by external beam radiation. However, the patient died after 7 months due to metastases to the liver, brain, heart, and skeletal system.[12] Recent genetic testing has, in some cases, revealed *BRAF*^{V600E} mutations.[15] These mutations are present in 15% of benign myopericytomas, 33% of which were multifocal/infiltrative or recurrent. Anti-*BRAF*^{V600E} therapy with vemurafenib disrupts angiogenetic and metabolic properties with downreglation of some extracellular matrix factors. Consequently, these molecules might be a useful adjuvant treatment for myopericytomas expressing *BRAF*^{V600E} mutations. Screening for these mutations is therefore recommended.

In our case report, the patient presented with a myopericytoma of the skin with atypical features. A broad resection was performed but no additional imaging studies were performed. In the years following, a tumour in the right kidney with similar histological features as the skin lesion but a higher degree of cytonuclear atypia occurred. We decided to perform a resection of a kidney metastasis of a malignant myopericytoma of the skin. It is possible that the kidney lesion was already present when excision of the skin lesion was performed and gradually grew until it became symptomatic. As the kidney lesion had higher cellularity, an elevated mitotic index and more cytonuclear atypia, as well as necrosis, we believe that the kidney tumour was a metastasis and not the primary tumour. As no *BRAF*^{V600E} mutation was found, and no other site of metastatic deposit was seen, no adjuvant therapy could be given. Three months after excision of the kidney metastasis a PET CT scan showed no evidence of metastases.

CONCLUSION

We report the first case of a malignant myopericytoma with metastases to the kidney. Therefore, the traditional view that urinary myopericytoma are benign primary lesions needs to be updated.

REFERENCES

1. Dictor M et al. Myofibromatosis-like hemangiopericytoma metastasizing as differentiated vascular smooth-muscle and myosarcoma. Myopericytes as a subset of "myofibroblasts". Am J Surg Pathol. 1992;16(12):1239-47.
2. Requena L et al. Cutaneous adult myofibroma: a vascular neoplasm. J Cutan Pathol. 1996;23(5):445-57.
3. Granter SR et al. Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of

tumors showing perivascular myoid differentiation. Am J Surg Pathol. 1998; 22(5):513-25.

4. Fletcher CDM et al. (eds), "Pericytic (Perivascular) Tumours", World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft tissue and bone (2002). Lyon: IARCPress, pp.135-40.

5. Mentzel T et al. Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 54 cases. Am J Surg Pathol. 2006;30(1):104-13.

6. Fisher C. Unusual myoid, perivascular, and postradiation lesions, with emphasis on atypical vascular lesion, postradiation cutaneous angiosarcoma, myoepithelial tumors, myopericytoma, and perivascular epithelioid cell tumor. Semin Diagn Pathol. 2013;30(1):73-84.

7. Lau SK et al. Myopericytoma of the kidney. Hum Pathol. 2010;41(10):1500-4.

8. Dhingra S et al. Renal myopericytoma: case report and review of literature. Arch Pathol Lab Med. 2012;136(5):563-6.

9. Zhao M et al. Benign perivascular myoid cell tumor (myopericytoma) of the urinary tract: a report of 2 cases with an emphasis on differential diagnosis. Hum Pathol. 2014;45(5):1115-21.

10. Zhang Z et al. Renal myopericytoma: A case report with a literature review. Oncol Lett. 2014;7(1):285-7.

11. Li J et al. Renal myopericytoma : a clinicopathologic study of six cases and review of the literature. Int J Clin Exp Pathol. 2015;8(5):4307-20.

12. McMenamin ME, Fletcher CD. Malignant myopericytoma: expanding the spectrum of tumours with myopericytic differentiation. Histopathology. 2002;41 (5):450-60.

13. Mainville GN et al. Primary malignant myopericytoma of the left atrium--a tumor of aggressive biological behavior: report of the first case and review of literature. Appl Immunohistochem Mol Morphol. 2015;23(6):464-9.

14. Holling M et al. Myopericytoma: A Series of 5 Cases Affecting the Nervous System. World Neurosurg. 2015. doi: 10.1016/j.wneu.2015.04.041. [Epub ahead of print].

15. Sadow PM et al. Role of BRAFV600E in the First Preclinical Model of Multifocal Infiltrating Myopericytoma Development and Microenvironment. J Natl Cancer Inst. 2014;106(8):dju182.

THE CURRENT STATE OF NEOADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER

***Oktay Üçer**

Department of Urology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
**Correspondence to uceroktay@yahoo.com*

Disclosure: The author has declared no conflicts of interest.
Received: 26.01.16 **Accepted:** 25.02.16
Citation: EMJ Urol. 2016;4[1]:88-93.

ABSTRACT

Radical cystectomy with extended pelvic lymph node dissection is the gold standard for the treatment of muscle-invasive bladder cancer (MIBC). Despite this definitive surgery, patients face a recurrence rate of approximately 50% 5 years after surgery. This high recurrence rate may be related to micrometastatic disease at the time of the surgery. Although the data to support adjuvant chemotherapy for treatment of these patients are insufficient, neoadjuvant chemotherapy (NAC) that includes cisplatin-based combination therapy for MIBC is recommended by the guidelines. This article reviews the current situation in NAC for the treatment of MIBC.

Keywords: Neoadjuvant chemotherapy (NAC), bladder cancer, muscle-invasive, radical cystectomy.

INTRODUCTION

Bladder cancer is one of the most common types of urinary tract malignancy representing the fourth most common cancer in men, with men accounting for 80% of all bladder cancer patients, and the eighth most common cancer in women.[1] Bladder cancer is a worldwide problem, with an estimated 429,800 new cases of bladder cancer and 165,100 deaths caused by the disease occurring in 2012. Incidence rates are highest in Europe, Northern America, Western Asia, and Northern Africa.[2] Approximately 90% of bladder cancers are the transitional cell or urothelial carcinoma type, and at initial diagnosis, 30% are found to be muscle-invasive bladder cancer (MIBC). Radical cystectomy and pelvic lymph node dissection remains the gold standard treatment for patients with MIBC.[3] The risk of recurrence following radical cystectomy for the treatment of MIBC is high, and correlates with stage.[4] Although radical cystectomy is the gold standard, it only provides 5-year survival in approximately 50% of patients.[5,6] Despite this being the gold standard treatment, patients with MIBC have about a 50% rate of recurrence.[6]

The risk of recurrence after radical cystectomy for clinically localised bladder cancer is high and stage dependent. Some authors suggest that the predominant cause of this high recurrence rate is occult micrometastases present at the time of radical cystectomy.[1] As a result, neoadjuvant chemotherapy (NAC) has been used to remove these occult micrometastases and improve unsatisfactory results for the last three decades.

In this review, we will discuss the current state of NAC for the treatment of MIBC. Only the results of randomised controlled clinical studies and meta-analyses for NAC have been reported in this article.

ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT CHEMOTHERAPY

NAC has been administered to patients with MIBC as part of bladder-preserving strategies aiming to both eliminate systemic microscopic disease early, and improve cancer-specific survival.[7] There are many advantages of administering NAC before radical cystectomy to patients with MIBC and cN0 M0. However, there are also some disadvantages of NAC, which cause most urologists to hesitate about its use. Although the data to

support adjuvant chemotherapy are insufficient, NAC, which includes cisplatin-based combination therapy, is recommended for the treatment of MIBC by the guidelines on muscle invasive and metastatic bladder cancer from the European Association of Urology.[5] Although only 1.2% of patients with MIBC cancer received NAC according to the data of the American National Cancer Data Base between 1998 and 2003,[8] this rate was reported as 12% by Feifer et al.[9] in 2011. Despite the recommendations associated with the use of NAC in patients with MIBC, and the outcomes of various randomised trials, the rate of patients receiving NAC has seen little increase.[5]

The potential advantages of NAC include:[5]

- Chemotherapy is delivered at the earliest time point for the treatment of micrometastatic disease
- It provides the opportunity to assess the chemosensitivity *in vivo*
- Patients have a higher tolerance and compliance to chemotherapy before radical cystectomy
- Patients may respond to NAC and reveal a suitable pathological status, determined mainly by achieving pT0, pN0, and negative surgical margins

The disadvantages of NAC include:[5]

- The definitive therapy delays in patients not sensitive to chemotherapy
- NAC may negatively affect surgical mortality and morbidity
- Overtreatment is a possible negative consequence for some patients

There is in fact no evidence for the first two disadvantages of NAC in the literature. Although published trials regarding the negative impact of delayed radical cystectomy only include series of chemo-naïve patients, delayed curative surgery might comprise the surgical results in patients not sensitive to chemotherapy. There are no studies showing that delayed radical cystectomy due to NAC has an adverse effect on survival in the literature.[5] In 2015, a retrospective study regarding delayed cystectomy was published. The impact of the timing of radical cystectomy from diagnosis of MIBC on survival in patients treated with NAC and radical cystectomy was evaluated in this study. The study showed that the timing of radical cystectomy in relation to the date of MIBC diagnosis did not significantly impact overall survival in patients with MIBC receiving NAC.[10]

Only one study, published in 2003, has reported a negative effect on surgical mortality and morbidity associated with NAC.[1] In this study, the survival and surgical outcomes of patients (N=317) treated with radical cystectomy and NAC (combination group) were compared with radical cystectomy alone (cystectomy group). They found that planned radical cystectomy was performed in 82% and 81% of the patients in the combination and cystectomy groups, respectively. There were no significant differences between the two groups in the rate of Grade 2 or 3 post-surgical complications, or deaths. Although there were no significant differences between the two groups in the rates of surgical mortality and morbidity, the median survival of the combination group (77 months) was longer than the cystectomy group (46 months). The percentage of surviving patients at Year 5 was 57% and 43% in the combination and cystectomy groups, respectively. Similarly, the data of the combined Nordic trial (N=620) showed that NAC did not have a significant effect on the rate of performable radical cystectomy. The cystectomy frequencies of the experimental and control groups were 86% and 87%, respectively.[3]

Overtreatment is a major problem associated with NAC as clinical staging of MIBC using bimanual examination, magnetic resonance imaging, or computed tomography may often result in over or understaging, and have a staging accuracy of only 70%.[11] Characterising responders to NAC is very important to minimise overtreatment and the unnecessary delay of curative therapy in MIBC. For patients with a complete response to NAC (pT0 N0), treatment has a major positive affect on overall survival.[12] Identification of responders to NAC utilising tumour molecular profiling in specimens obtained via transurethral resection of the bladder may guide the use of NAC.[13] Many studies have investigated imaging techniques using the early identification of responders. The results of these studies showed that magnetic resonance imaging, computed tomography, or positron emission tomography could not accurately predict response to NAC.[14-16]

NEOADJUVANT CHEMOTHERAPY REGIMENS

Many chemotherapy regimens have been used for the treatment of MIBC before radical cystectomy. The guidelines recommend the use of platinum-based combination chemotherapy regimens as

neoadjuvant therapy in those patients.[5] The combination regimens tested were methotrexate, vinblastine, adriamycin (doxorubicin)/(epirubicin), and cisplatin (MVA[E]C); cisplatin, methotrexate, and vinblastine (CMV); cisplatin and methotrexate (CM); cisplatin/adriamycin, cisplatin, and 5-fluorouracil (5-FU); and carboplatin, methotrexate, and vinblastin. MVAC is the only regimen with Level I data at this time.[1] The most current retrospective and pooled studies have reported that efficacy is similar between gemcitabine, cispaltin (GC), and MVAC.[17-20] The data from these studies showed that although there were no differences between the response rate to GC and MVAC, the rate of chemotherapy-related complications, such as anaemia, neutropenia, neutropenic fever, and mucositis in patients receiving GC were significantly decreased. However, there have been no randomised prospective studies comparing GC with MVAC regimens in the literature.

RANDOMISED CLINICAL TRIALS AND META-ANALYSES FOR NEOADJUVANT CHEMOTHERAPY

Several randomised Phase III trials have published outcomes of NAC for the treatment of MIBC.[1,21-28] The data of these studies are summarised in Table 1. Shipley[25] and Abol-Enein[26] evaluated the impact of two or three cycles CMV on overall survival at 5 years. However, these studies found that there were no statistically significant benefits of chemotherapy. Sengelov[24] and NORDIC II[23] investigated the effectiveness of three cycles CM before surgery or radiotherapy. The results of these two studies were similar to the results of earlier studies; there were no differences in overall survival between the experimental and control arms. Wallace[27] and Martínez-Piñeiro[28] used three cycles of cisplatin alone as NAC in their studies, and reported no significant benefit of this course of treatment.

Table 1: Randomised Phase III trials with regard to neoadjuvant chemotherapy for the treatment of muscle-invasive bladder cancer.

Trial	Comparison (n)	Stage	CT regime	Median survival (months)	OS at 5 years (%)	OS at 10 years (%)
Grossman et al.[1] (2003)	S (154)	T2-4a	3 cycles	46	43	-
	CT+S (153)	N0 M0	MVAC	77, p=0.05	57, p=0.06	
International Collaborations[21] (2011)	S/R (485)	T2-4a	3 cycles	37	43	30
	CT+S/R(491)	N0/XM0	CMV	44	49	36
GUONE[22] (1998)	S (102)	T2–T4,	MVAC	-	*No significant difference	-
	CT+S (104)	N0 M0				
NORDIC 2[23] (2002)	S (154)	T2-T4a	3 cycles	-	53	-
	CT+S (155)	NXM0	CM		46, p=0.23	
Sengeløv et al.[24] (2002)	S/R (75)	T2-T4b	3 cycles	45.8	29	-
	CT+S/R (78)	NX-3MO	CM	82.5, p=0.76	29	
Shipley et al.[25] (1998)	R (62)	T2-T4a	3 cycles	-	49	-
	CT+R (61)	NX M0	CM		48	
Abol-Enein et al.[26] (1997)	S (total= 196)	T2-T4a	2 cycles	-	No significant difference	-
	CT+S	NxM0	CMV			
Wallace et al.[27] (1991)	R (76),	T2-T4	3 cycles	-	No significant difference	-
	CT+R (83)	NX M0	C			
Martínez-Piñeiro et al.[28] (1995)	S (55)	T2-T4a	3 cycles	No significant difference	-	-
	CT+S (41)	Nx-2M0	C			

*overall survival at 3 years

CT: chemotherapy; S: surgery; R: radiotherapy; MVAC: methotrexate, vinblastine, doxorubicin/epirubicin, cisplatin; CMV: cisplatin, methotrexate, vinblastine; CM: cisplatin, methotrexate; C: cisplatin; OS: overall survival.

Despite the negative results reported by earlier randomised controlled studies, the results of two studies[1,21] and three meta-analyses[29-31] have successfully demonstrated a survival benefit in the use of NAC for the treatment of patients with MIBC. The most recent and largest study was published by the International Collaboration of Trialists, and included 976 patients with MIBC. This study demonstrated a statistically significant 16% reduction in the risk of death (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.72–0.99; p=0.037), corresponding to an increase in 10-year survival from 30% to 36% after NAC. Many randomised controlled studies have shown a statistically insignificant increase in overall or disease-free survival at 5 years. Grossman et al.[1] randomised patients with MIBC to either NAC plus cystectomy or cystectomy alone. Patients in the experimental arm received three cycles MVAC before cystectomy. Median survival in the experimental and control arms were 77 and 46 months (p=0.05), respectively, and overall survival was 57% and 43% at 5 years (p=0.06), respectively.

The three most recent meta-analyses with regard to NAC for the treatment of MIBC were published between 2003 and 2005. The Advanced Bladder Cancer Meta-analysis Collaboration[29] analysed updated data for 2,688 individual patients from 10 randomised controlled trials. The results of the first meta-analysis showed that platinum-based combination chemotherapy provides a significant benefit to overall survival (HR: 0.87, 95% CI: 0.78–0.98, p=0.016). It was also demonstrated that NAC provides a 13% reduction in risk of death, 5% absolute benefit at 5 years, and an increase in overall survival from 45% to 50%.[28] The second meta-analysis was comprised of the data of 2,605 patients with MIBC from 11 randomised controlled trials. They noted an absolute overall survival benefit of 6.5% (95% CI: 2–11%) from 50% to 56.5% regarding platinum-based combination chemotherapy.[30] The last meta-analysis for NAC analysed the data of 3,005 patients in 11 randomised controlled trials.[31] They noticed significant overall and disease-free survival benefits with regard to platinum-based combination chemotherapy (HR: 0.86, 95% CI: 0.77–0.95, p=0.003 and HR: 0.78, 95% CI: 0.71–0.86, p<0.0001, respectively). These are equivalent to a 5% and 9% absolute improvement in overall survival and disease-free survival at 5 years, respectively. They consequently reported that their findings provided the best available evidence in support of the use of NAC for the patients with MIBC cancer.

More modern chemotherapy regimens, such as GC, have shown similar pT0/pT1 rates as MVAC in recent retrospective series and pooled data analyses, but have not been used in randomised controlled trials. Dash et al.[19] retrospectively investigated patients with MIBC who received neoadjuvant GC before radical cystectomy. They suggested that neoadjuvant GC is feasible and allows for timely drug delivery. They also reported that the proportion of GC-treated patients, whose primary tumours were downstaged, with prolonged disease-free survival and minimal or no residual disease, was similar to MVAC-treated patients. Lee et al.[18] compared pathologic outcomes after treatment with GC versus MVAC in the neoadjuvant setting. They observed similar pathologic response rates for GC and MVAC in this cohort of patients with MIBC. This study supports the use of GC as an alternative regimen in the neoadjuvant setting. Yuh et al.[17] evaluated the effectiveness of neoadjuvant GC for MIBC based on currently published studies. They reported that GC yielded appreciable pathological response rates in patients with MIBC. They also suggested that since pathological response has been implicated as a potential surrogate for survival in MIBC, these data suggested that neoadjuvant GC might warrant further prospective assessment.

Adjuvant chemotherapy for the treatment of patients with MIBC (pT3/pT4 and/or N+ M0) is under debate and still infrequently used. There is limited evidence from adequately conducted randomised Phase III trials in favour of the routine use of adjuvant chemotherapy. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.[32-34] In contrast, Tjokrowidjaja et al.[35] presented the survival benefits of adjuvant and NAC in MIBC in the 2013 ASCO Annual Meeting. They analysed the data of 21 randomised controlled trials (9 adjuvant and 12 NAC) and presented the results of the meta-analysis. They consequently noted that chemotherapy, both adjuvant and neoadjuvant, improves survival in MIBC.

CONCLUSION

Platinum-based NAC for treatment of patients with MIBC is well tolerated (with minimal-to-moderate morbidity and no mortality) and improves overall survival (5–8% at 5 years). Limitations exist in

regard to patient selection, current development of surgical techniques, and current chemotherapy combinations, though there is a major impact on overall survival in responders who show complete response (pT0 N0). However, no techniques are available to choose patients who have a higher probability of benefitting from NAC. Consequently, the guidelines and meta-analyses on the treatment of MIBC recommend using NAC (cisplatin-based combination therapy) for patients with T2-T4a, cN0 M0 bladder cancer. Despite the recommendations associated with the use of NAC in patients with MIBC and the outcomes of randomised trials, the rate of patients receiving NAC has seen little increase. The reason for this low rate might be due to some concerns from urologists, such as delayed curative surgery treatment, and negative impact on peri and post-operative mortality and morbidity of chemotherapy. However, there is much evidence in the literature that show that NAC is not associated with these negative outcomes. Therefore, the rate of the use of NAC in patients with MIBC may increase in future.

REFERENCES

1. Grossman HB et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859-66.

2. Torre LA et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

3. Sherif A et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol. 2004;45(3):297-303.

4. Stein JP et al. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol. 2006;24(3):296-304.

5. Witjes JA et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol. 2014;65(4):778-92.

6. Porter MP et al. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol. 2011;29(3):252-8.

7. Heidenreich A. Muscle-invasive urothelial carcinoma of the bladder: neoadjuvant chemotherapy enables organ-preserving therapy in carefully selected patients. Eur Urol. 2008;54(1):21-3.

8. David KA et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol. 2007;178(2):451-4.

9. Feifer A et al. Multi-institutional quality-of-care initiative for nonmetastatic, muscle-invasive, transitional cell carcinoma of the bladder. Abstract 240. Genitourinary Cancers Symposium, Orlando, Florida, USA, 17-19 February 2011.

10. Park JC et al. A Retrospective Analysis of the Effect of Time from Diagnosis to Cystectomy on Survival in Patients with Muscle Invasive Bladder Cancer Receiving Neoadjuvant Chemotherapy. J Urol. 2015. doi: 10.1016/j.juro.2015.11.024. [Epub ahead of print].

11. Sternberg CN et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer. 2003;97(7):1644-52.

12. Rosenblatt R et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012;61(6):1229-38.

13. Takata R et al. Validation study of the prediction system for clinical response of M-VAC neoadjuvant chemotherapy. Cancer Sci. 2007;98(1):113-7.

14. Letocha H et al. Positron emission tomography with L-methyl-11C-methionine in the monitoring of therapy response in muscle-invasive transitional cell carcinoma of the urinary bladder. Br J Urol. 1994;74(6):767-74.

15. Krajewski KM et al. Optimisation of the size variation threshold for imaging evaluation of response in patients with platinum-refractory advanced transitional cell carcinoma of the urothelium treated with vinflunine. Eur J Cancer. 2012;48(10):1495-502.

16. Nishimura K et al. The effects of neoadjuvant chemotherapy and chemo-radiation therapy on MRI staging in invasive bladder cancer: comparative study based on the pathological examination of whole layer bladder wall. Int Urol Nephrol. 2009;41(4):869-75.

17. Yuh BE et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol. 2013;189(5):1682-6.

18. Lee FC et al. Pathologic Response Rates of Gemcitabine/Cisplatin versus Methotrexate/Vinblastine/ Adriamycin/ Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. Adv Urol. 2013;2013:317190.

19. Dash A et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer. 2008;113(9):2471-7.

20. Weight CJ et al. Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. Cancer. 2009;115(4):792-9.

21. Griffiths G et al.; International Collaboration of Trialists et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011;29(16):2171-7.

22. Bassi P et al. Neoadjuvant M-VAC chemotherapy of invasive bladder cancer: The G.U.O.N.E. multicenter phase III trial. Eur Urol. 1998;33(Suppl 1):142.

23. Sherif A et al.; Nordic Urothelial Cancer Group. Neoadjuvant cisplatinmethotrexate chemotherapy for invasive bladder cancer-- Nordic cystectomy trial 2. Scand J Urol Nephrol. 2002;36(6):419-25.

24. Sengeløv L et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. Acta Oncol. 2002;41(5):447-56.

25. Shipley WU et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol. 1998;16(11):3576-83.

26. Abol-Enein H et al. Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled prospective randomized study. Br J Urol. 1997;79(Suppl 4):174.

27. Wallace DM et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol. 1991; 67(6): 608-15.

28. Martínez-Piñeiro JA et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol. 1995;153(3 Pt 2):964-73.

29. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003;361(9373):1927-34.

30. Winquist E et al. Genitourinary Cancer Disease Site Group, Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol. 2004;171(2 Pt 1):561-9.

31. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48(2):202-5.

32. Leow JJ et al. Adjuvant chemotherapy for invasive bladder cancer: A 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol. 2014;66(1):42-54.

33. Cognetti F et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012;23(3):695-700.

34. Stadler WM et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. J Clin Oncol. 2011;29(25):3443-9.

35. Tjokrowidjaja et al. Does chemotherapy improve survival in muscle-invasive bladder cancer (MIBC)? A systematic review and meta-analysis (MA) of randomized controlled trials (RCT). Abstract 4544. 2013 ASCO Annual Meeting Chicago, 31 May–4 June.

PENILE ENHANCEMENT SURGERY: AN OVERVIEW

***Marta R. Bizic,[1] Miroslav L. Djordjevic[1,2]**

1. University Children's Hospital, Belgrade, Serbia
2. School of Medicine, University of Belgrade, Belgrade, Serbia
**Correspondence to martabizic@uromiros.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 08.12.15 **Accepted:** 10.03.16
Citation: EMJ Urol. 2016;4[1]:94-100.

ABSTRACT

Penile size is a frequently observed concern in men of all ages. The way in which some men see their personality is defined, appraised, or reflected by their penis, with the view that 'bigger is better', is termed 'phallocentrism'. In this review article, we assess the literature and evaluate the evidence on what is 'normal' in relation to penile size, and evaluate techniques for penile lengthening and girth augmentation with emphasis on the possible benefits and complications of the procedures reviewed.

Keywords: Penis, small penis syndrome (SPS), penile enhancement, penis augmentation, penis lengthening, penile reconstruction surgery.

INTRODUCTION

The penis has been regarded as a symbol of masculinity throughout history, hence penile size has long been a source of anxiety for many men. Though the majority of men fall within the 'normal' range of penile length, the concerns regarding penile size and girth may cause low self-esteem, sexual dysfunction, depression, and other psychiatric disorders.

For centuries, men have undergone many different processes in an effort to enlarge and enhance their penises. For instance, the Sadhus, holy men of India, and men of the Caramoja tribe in Uganda use weights to increase the length of their penises. The men of the Dayak tribe from Borneo were the first to introduce penile piercing, inserting decorations for their partner's pleasure.[1] Evidence suggests that the ancient Greeks and Romans also fixated on the penis and its importance; this can be observed in some of the paintings and statues from that era.[2]

The tendency of some men to look for their identity in their penis with the view that 'bigger is better' is reflected by the term 'phallic identity', as introduced by Vardi, or 'phallocentrism'.[1,3] The notion of small penises and the influence of different media on sexual issues, which just a few decades ago were considered taboo and socially unacceptable for discussion in public, has led to the development of a number of different modes of penile enhancement. Because of this, the psychiatric term 'penile dysmorphophobia' was introduced to describe an abnormal perception of penile size, when the penis itself is within what is considered to be the normal size range.[4]

METHODS

We searched the MEDLINE database for articles describing various techniques for penis enhancement using the following keywords: penis, small penis syndrome, penile enhancement, penis augmentation, penis lengthening, and penile reconstruction surgery. Only articles written in the English language were included; articles in which the only recommendation for penis augmentation was phalloplasty using extragenital tissue were excluded.

REVIEW

Penile Size

The question of what is considered a 'normal' penile size has remained ambiguous, lacking a consensus until recently. Recently, there have been several studies published on penile length and girth and what should be considered a normal penis size or a micropenis.

The first studies to address penile size were published in the 19th century, and the publication of such articles continued thereafter.[2] The authors of these studies measured various aspects of penis size, including penis length in flaccid, flaccid stretched, and erect states, and penile girth in both flaccid and erect states. The variability of the recorded values depended on the population included in the study, as well as on the measuring technique.[5] In these studies, average penis length was estimated to be approximately 9 cm when flaccid, and ranged from 12–13 cm and 14–16 cm in flaccid stretched and erect states, respectively. In regard to girth, the average circumference ranged from 9–10 cm when flaccid and from 12–13 cm in the erect state.[2,5-10]

The studies presented demonstrated that younger men usually have longer, wider penises.[9] One study also showed a large statistical difference between homosexual and heterosexual men in terms of penis girth and length, with homosexual men reporting larger penises than heterosexual men.[11] There remains a need for further investigation of penis size among different races, as there are a lack of studies focussing on this aspect.

Unbiased standardisation is needed to make the comparison of data more accurate. In all cited studies, we saw differences in the technique used to measure penis size. There now exists a general consensus that penile length should be measured on the dorsal side of the penis, from the penopubic junction to the tip of the glans in the flaccid, flaccid stretched, and erect states. Likewise, penile girth should be measured around the middle of the shaft of the penis in both the flaccid and erect state. The measurements should be made by a single physician and should not use self-reported questionnaire data. With the exception of Wessells' records,[9] no study performed these measurements under all of these conditions. Given the huge variability in penile size and penile extensibility, penile evaluation should, without a doubt, be performed in flaccid and stretched states, with the specific final objective of reaching a consensus on the definition of what penile size encompasses and the associated method of measurement. After considering these studies, Dillon et al.[2] concluded that with respect to penile length, average flaccid penis size was approximately 9.0–9.5 cm, and 14.5–15 cm in the maximally stretched state. Average erect penis length ranged from 12.8–14.5 cm, and girth approximately 10.0–10.5 cm. By applying these findings, we were able to define potential candidates for penile enhancement surgery as men who are two standard deviations below the average size, and patients with a flaccid penile length of <5 cm and girth <8 cm.[2]

Micropenises

The term micropenis refers to a series of congenital and acquired conditions that result in an abnormally short penis; this state can be associated with functional and psychological problems.[12]

A true micropenis results from hormonal disruption during gestational development and results in either an isolated micropenis, or a micropenis as part of a sexual development disorder.[13] The hormonal causes of micropenis development can be classified into three groups: hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, and idiopathic hypogonadism.[13] As patients with a true micropenis can also suffer from emotional and psychological crises due to the functional problems associated with small penis size, a multidisciplinary approach is essential for diagnosis and treatment. All patients in whom there is a suspicion of a micropenis condition should undergo karyotyping and hormonal evaluation, as well as a detailed examination by an endocrinologist. Nonsurgical treatment of the true micropenis in infancy involves the correction of reversible metabolic defects. However, surgical treatment such as gender reassignment or penis augmentation surgery in childhood should be carefully evaluated.[12]

The development of an acquired micropenis involves penile shortening, which can occur as a consequence of diseases such as prostate cancer, priapism, Peyronie's disease, erectile dysfunction, Fournier's gangrene, lichen sclerosus, penile cancer, or trauma. Penile shortening happens as a result of corporal fibrosis due to chronic hypoxia, anatomical shortening, loss of tissue elasticity after penile surgery, creation of plaque in Peyronie's disease, or after radical surgery for benign or malignant tumours. In many cases, reconstructive surgery offers patients a feasible option for restoring penis length and function (penile reconstructive surgery, grafting, penile prosthesis, etc.). Nevertheless, adequate counselling is necessary to create realistic post-operative expectations among these patients and to support their long-term rehabilitation.[12]

Ghanem et al.[14] used a structured protocol for the management and counselling of 250 men who complained of a small penis size. Examination

revealed that 81.6% patients had no physical abnormality and presented with a normal-sized penis. After application of a structured management and counselling protocol, 96.4% of patients agreed that their penis size concerns had been eliminated. Only nine patients decided to seek further surgical treatment. Of the nine patients who underwent penis augmentation surgery, only one true micropenis patient and two normal-sized penis patients were satisfied with the results of the surgery, with the remainder of the patients reporting poor satisfaction with the achieved size. The results of this study suggest that the majority of men complaining of a small penile size are misinformed, while some suffer from body dysmorphic disorder (BDD) in the form of penile dysmorphophobia. In this population of dysmorphic men, we can achieve better results through counselling and support from psychologists and psycho-sexologists, than by offering surgical augmentation.[14]

Penile Augmentation Procedures

There are several distinct types of penile augmentation surgery, each aimed at a different outcome; some increase length or girth, and a third group aims to achieve both of these objectives. In addition, there are several related plastic surgery procedures aimed at reconstructing the skin surrounding the penis. In a position statement draft regarding penis augmentation surgery, the Sexual Medicine Society of North America has concluded that penile lengthening and girth enhancement surgery can only be regarded as experimental surgery, as there are no peer-reviewed, objective, or independently monitored studies or other data that prove the safety or efficacy of penis lengthening and girth enhancement surgery.[2,15]

As Ghanem et al.[14,16] state, many men complaining of small penis syndrome (SPS) have a misconception of what normal penis size is, but there are also those who suffer from BDD. In all of these patients, education regarding normal variations in penile size is very important, as is psychotherapy.[14,16] In cases in which the patient is still considering surgery after completing psychological counselling, there are several surgical options available which will be reviewed in this article.

Penile Lengthening

Several techniques have been described to increase penis length. Some patients complain of SPS as a result of abundant suprapubic fat tissue or a protruding abdomen, which can be solved by liposuction and/or suprapubic lipectomy. This achieves a visual lengthening of the penis.[1,17,18] In cases where the patient requires further penile lengthening, one proposed surgical technique is to detach the suspensory ligament of the penis. Dissection of the suspensory ligament enables the penis to move forward and to appear longer in the flaccid state by 1.5–2 cm. Reattachment of the ligaments and *de novo* penile shortening need to be avoided. Alter et al.[19] recommend suturing the vascularised flap from the lipomatous tissue of the spermatic cord to the pubic periosteum, and Li et al.[20] suggest suturing a small silicone testicular prosthesis to the base of the pubis to prevent penile retraction.[1,19,20] All authors recommend the use of special penile extenders to keep the penis separated from the pubis, which also allows the penis to heal in the most extended position possible.

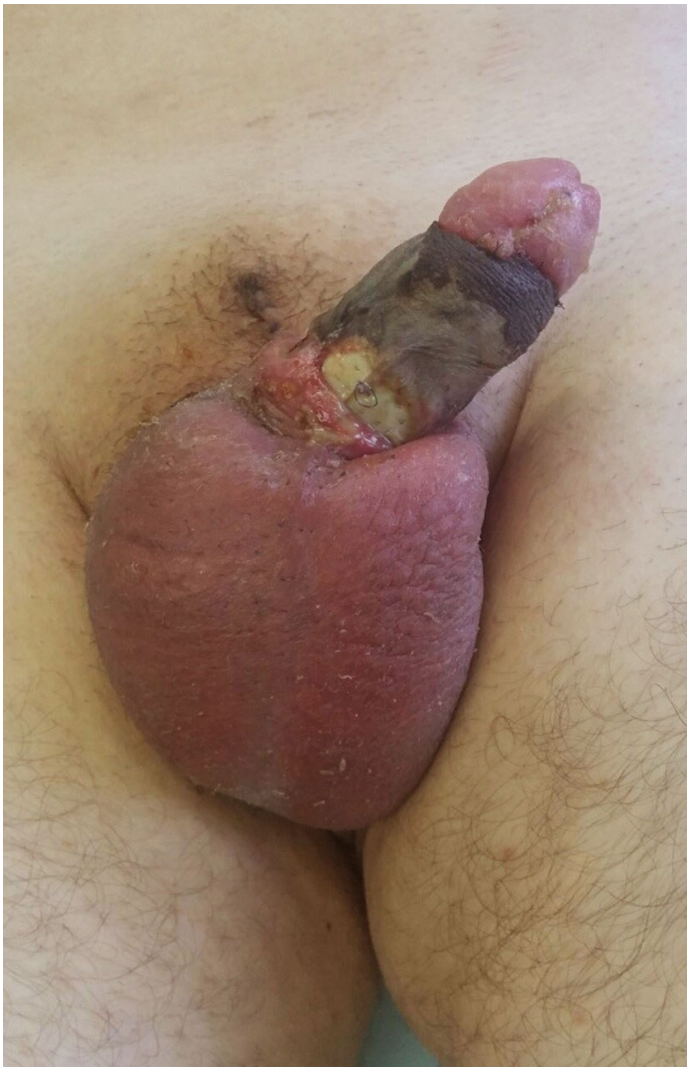


Figure 1: Severe penile skin necrosis after penile enhancement with paraffin injections.

This procedure is often combined with inverted V-Y plasty or Z-plasty to increase penile length further, or use of the circumcision approach to prevent visible scarring on the lower abdomen.[21] Inverted V-Y plasty was first described by Long, and later modified by Roos and Lissoos[22] in 1994. They described the use of suspensory ligament release resulting in an increase in length of 4 cm in their group of patients.[1,22] Lower abdominal Z-plasty produces the best results due to low risk of scrotal skin sliding onto the penile shaft.[19] The role of a suspensory ligament is very important in penile stabilisation during erection to create a specific angle for vaginal penetration and sexual intercourse; dissection of the ligament can lead to a downward position of the penis in the erect state.

In patients with penoscrotal webbing that results in a hidden penis, the reconstruction of the penoscrotal angle and scrotal and penile skin by Z-plasty can resolve the problem without additional procedures for penile lengthening. In 2007, Alter[23] reported that overly aggressive circumcision in which too much ventral penile skin is excised results in penile shortening due to penoscrotal webbing in the majority of patients.

In 2000, Perovic and Djordjevic[24] reported penile lengthening in 19 patients using the penile disassembly technique, a technique involving the placement of the autologous rib cartilage between the corpora cavernosa and glans cap; however, long-term follow-up data are not available.[24]

A special group of patients requiring penile elongation procedures are those with epispadias and bladder extrophy.[2] These patients receive surgery to repair the bladder and penis during early childhood and are monitored by paediatric urologists. The most commonly used procedure for epispadias repair is the Cantwell–Ransley staged procedure.[25] In rare cases, patients report short penises with severe dorsal penile curvatures and short urethras that require secondary repair. In 2013, Djordjevic et al.[26] reported good functional and cosmetic results in 19 of 23 patients with failed epispadias repair in childhood, with an improvement in penile length of 2.7–6.6 cm in the erect state.[26]

Penile Girth Enhancement

Penis girth enhancement procedures are even more controversial than penis lengthening procedures. There is no standardised recommendation or indication for penile girth enhancement in the medical literature, and no guidelines have been proposed for such an intervention.[2,8] The goal of such a procedure would be a symmetrical increase in the girth of the penis, and though there is no standardised process, methods with this objective have been described and used either by patients themselves or by doctors such as plastic surgeons, urologists, and dermatologists.

Instillation of different exogenous substances under the skin for penile girth enlargement is very common in some culture settings and is present even today.[27] Injection of liquid and melted paraffin was introduced around the year 1900 to enlarge penis circumference. Paraffin injection causes an intense inflammatory reaction leading to granulomas, ulcers, and skin necrosis, with the risk of penis loss (Figure 1).[28,29]

Liquid injectable silicone (LIS) became very popular in aesthetic surgery in the 1940s and appeared to be relatively safe.[30] Inspired by early results, surgeons started injecting LIS for penile girth enhancement but stopped following the appearance of silicone migration and the development of complications such as erectile dysfunction, significant and prolonged swelling, penile curvature, and late granulomatous reactions.[31,32] However, despite the side effects, Yacobi et al.[33] reported full short-term satisfaction in 324 patients injected with LIS with an average augmented penis circumference of 2.6 cm.

Injection of autologous fat was initially thought to be a promising procedure for penis girth enhancement. Panfilov[34] reported a mean girth enhancement of 2.65 cm in 88 patients following the injection of 40–68 mL of autologous fat. Following this, in 2012, Kang et al.[35] reported an average increase in girth of 2.71 cm following injection of 25–49 mL of autologous fat. There are fewer complications associated with the injection of a small amount of fat tissue with a minimal increase in girth compared with the injection of larger amounts. Increasing the amount of injected fat results in a more significant immediate girth enhancement, but is also associated with a much higher risk of complications. It has been proven that >50% of injected fat is absorbed, and the injection of large amounts can cause severe penile deformities, necrosis, and calcification of the fat tissue, as well as asymmetry.[1,19]

Kim et al.[36] reported satisfying results in an 18-month follow-up of 15 men treated with polymethyl methacrylate and cross-linked dextran for penile

augmentation without side effects or migration of the instilled material. Further follow-up and larger series of patients are needed to prove the safety of this penile enhancement procedure.[36]

After observing the developments in aesthetic surgery, urologists and plastic surgeons started to use injectable hyaluronic acid gel for penile and glans augmentation.[37] Perovic et al.[38] reported good results of enlargement and sculpturing of small and deformed glans in 8 of 9 patients who were subjected to this technique. The authors did not report any side effects from the hyaluronic acid gel. In same year, Kim et al.[39] reported a high satisfaction rate among 187 men who underwent this glans enlargement procedure with an increase in glanular circumference of 1.5 cm at 1-year follow-up. Kwak et al.[40] followed 38 patients for a period of 5 years and did not report a significant difference in patients' visual estimation of glans circumference. The advantages of hyaluronic acid gel are increased tissue longevity and possible reinjection in cases of long-term volume loss, with few studies' reporting immediate or delayed adverse effects in association with its use.

Another advancement is the use of dermal fat grafts, which, according to Alter,[19] are considered to be superior to the fat injection procedure and have been used with success in plastic surgery.

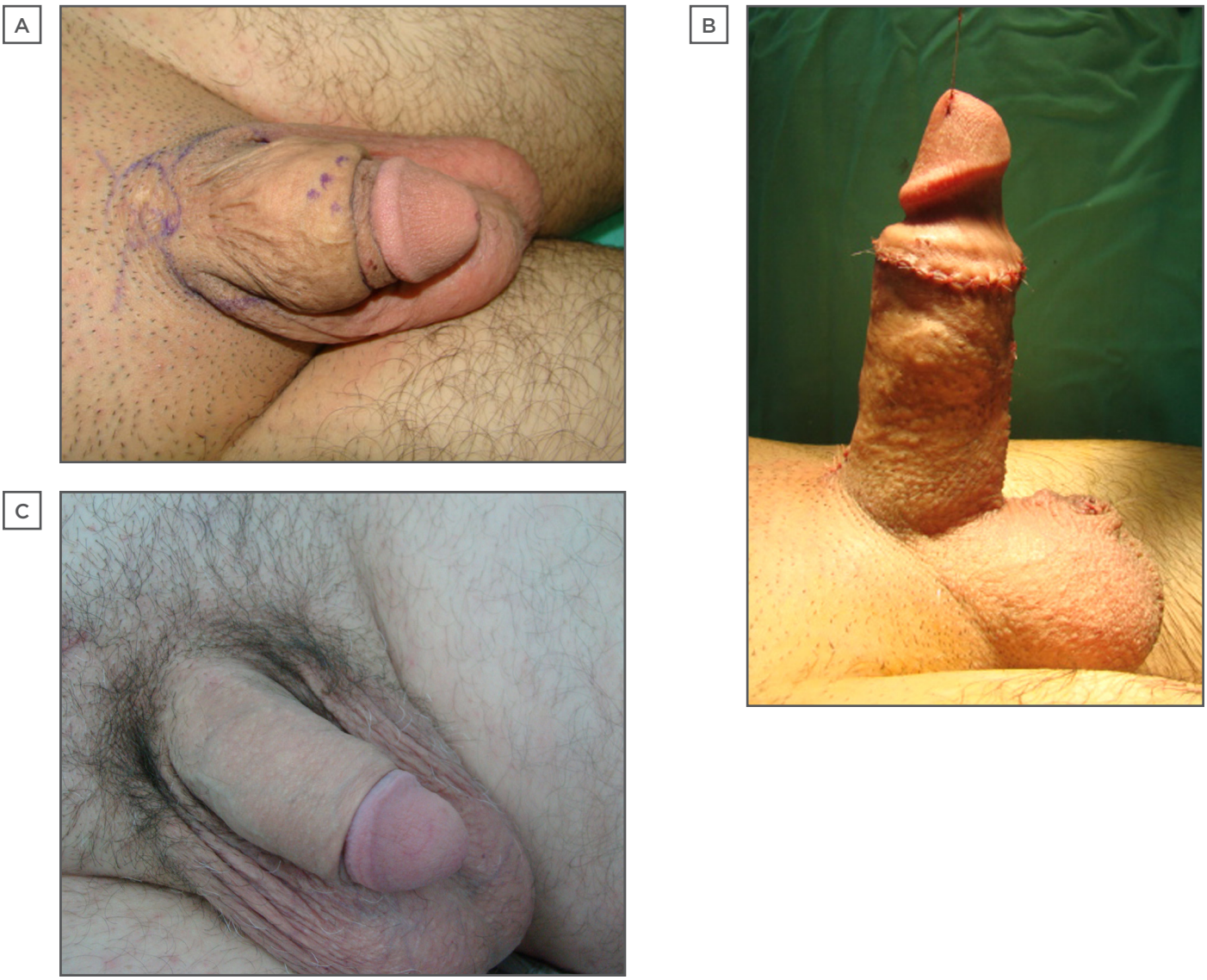


Figure 2: Penile enhancement by poly(lactic-co-glycolic acid) scaffolds.
A) Outcome after penile enlargement by lipofilling. Penis is shortened and deformed; B) Appearance after redo surgery: two poly(lactic-co-glycolic acid) scaffolds pretreated with autologous fibroblasts are placed around the penile body. Penoscrotal webbing is corrected; C) Appearance at 6-month follow-up: good contour of the augmented penis is achieved. Difference before and after surgery is clear.

Alter also states that circumferential placement of the dermal graft without covering the urethra is the ideal technique with an average girth enhancement between 2.5–5 cm.[19] Nonetheless, inadequate graft harvesting, local infection, graft fibrosis resulting in penile curvature, and subsequent shortening made this technique unacceptable for penile girth enhancement. These findings opened the door to other researchers in this field to present their techniques.[17]

In 2002, Austoni et al.[41] performed bilateral saphenous graft augmentation of the penis in 39 patients with penile hypoplasia or penile dysmorphophobia. Shaeer et al.[42] have recently reported superficial circumflex iliac artery and vein flap as a reliable option for long-lasting and sizeable penile girth augmentation. However, these procedures are thought to be an invasive and aggressive treatment for patients with penile dysmorphophobia.

The use of acellular inert dermal matrices (allografts) is common in plastic surgery, especially in breast reconstruction. The use of allografts in penile girth enhancement surgery is believed to have potential in providing good cosmetic results with respect to penile symmetry and durability, and to present with a lower complication rate compared with the dermal fat graft technique. The technique includes placement of the allograft around the penile shaft at the level of the deep fascia of the penis. However, in a study by Solomon et al.[43] 20 patients developed a graft infection, which was either treated solely by antibiotics or required additional surgery, while 3 patients suffered graft loss. Due to the lack of new data on allograft use in penile girth enhancement, this procedure still needs to be considered experimental.[1]

Development of tissue engineering also led to its use in penis girth enhancement. We published the use of poly(lactic-co-glycolic acid) (PLGA) scaffolds pretreated with autologous fibroblasts for penis girth enhancement.[44] The pretreated scaffolds were placed between the dartos and deep fascia without covering the urethra following penile degloving. Of the 84 patients who entered the study, 70% were completely satisfied. Mean penile girth augmentation was 3.15 cm in the flaccid state and 2.47 cm in the erect state (Figure 2a, 2b, and 2c).[45] Complications included local infection, local skin necrosis, and seroma, which were treated conservatively. During the repeat procedure, we obtained samples of newly formed tissue 9–12 months after previous penis girth enhancement with PLGA-pretreated scaffolds. Microscopic evaluation showed the presence of vascularised loose connective tissue with an abundance of collagen fibres, fibroblasts, and inflammatory cells, indicating active neovascularisation and fibrillogenesis.[46] Jin et al.[47] obtained similar results after treating 69 patients with SPS, of which 94.2% were satisfied with the procedure. Further studies and long-term follow-up are also needed for this treatment.

CONCLUSION

The topic of penile size is a contentious issue for many men, regardless of their age. Penis size is considered a symbol of masculinity and sexual power and has great impact on self-esteem and sexual function. Based on the current status of science, penis enhancement surgery is still considered to be experimental and its indications are still a matter of medical and ethical debate.

As there is still a significant percentage of patients that are dissatisfied following penis enhancement procedures, preoperative counselling with a psychologist and sexologist should be considered to moderate patients' expectations from penis augmentation surgeries. In this respect, we believe that tissue engineering presents a new opportunity in penis augmentation surgery that should be developed in the future.

Acknowledgements

This paper is supported by the Ministry of Science and Technological Development, Republic of Serbia, Project No. 175048.

REFERENCES

1. Vardi Y et al. A critical analysis of penile enhancement procedures for patients with normal penile size: surgical techniques, success, and complications. Eur Urol. 2008;54(5):1042-50.

2. Dillon BE et al. Penile size and penile enlargement surgery: a review. Int J Impot Res. 2008;20(6):519-29.

3. Vardi Y, Lowenstein L. Penile enlargement surgery – fact or illusion? Nat Clin Pract Urol. 2005;2(3):114-5.

4. Mondaini N et al. Penile length is normal in most men seeking penile lengthening procedures. Int J Impot Res. 2002;14(4):283-6.

5. Aslan Y et al. Penile length and somatometric parameters: a study in healthy young Turkish men. Asian J Androl. 2011;13(2):339-41.

6. Bondil P et al. Clinical study of the longitudinal deformation of the flaccid penis and of its variations with aging. Eur Urol. 1992;21(4):284-6.

7. Ponchietti R et al. Penile length and circumference: a study on 3,300 young Italian males. Eur Urol. 2001;39(2):183-6.

8. da Ros C et al. Caucasian penis: what is the normal size? J Urol. 1994;151:323A.

9. Wessells H et al. Penile length in the flaccid and erect states: guidelines for penile augmentation. J Urol. 1996;156(3):995-7.

10. Söylemez H et al. Relationship between penile size and somatometric parameters in 2276 healthy young men. Int J Impot Res. 2012;24(3):126-9.

11. Bogaert AF, Hershberger S. The relation between sexual orientation and penile size. Arch Sex Behav. 1999;28(3):213-21.

12. Kayes O et al. Therapeutic strategies for patients with micropenis or penile dysmorphic disorder. Nat Rev Urol. 2012;9(9):499-507.

13. Tsang S. When size matters: a clinical review of pathological micropenis. J Pediatr Health Care. 2010;24(4):231-40.

14. Ghanem H et al. Structured management and counseling for patients with a complaint of a small penis. J Sex Med. 2007;4(5):1322-7.

15. Sexual Medicine Society of North America. Position Statement: Penile Lengthening and Girth Enhancement Surgery. Available at: http://www.smsna.org/V1/about/position-statements. Last accessed: 8 December 2015.

16. Ghanem H et al. Position paper: Management of men complaining of a small penis despite an actually normal size. J Sex Med. 2013;10(1):294-303.

17. Spyropoulos E et al. Augmentation Phalloplasty Patient Selection and Satisfaction Inventory: a novel questionnaire to evaluate patients considered for augmentation phalloplasty surgery because of penile dysmorphophobia. Urology. 2007;70(2):221-6.

18. Wylie KR, Eardley I. Penile size and the 'small penis syndrome'. BJU Int. 2007;99(6):1449-55.

19. Alter GJ. Augmentation phalloplasty. Urol Clin North Am. 1995;22(4):887-902.

20. Li CY et al. Penile suspensory ligament division for penile augmentation: indications and results. Eur Urol. 2006;49(4):729-33.

21. Mertziotis N et al. Is V-Y plasty necessary for penile lengthening? Girth enhancement and increased length solely through circumcision: description of a novel technique. Asian J Androl. 2013;15(6):819-23.

22. Roos H, Lissoos I. Penile lengthening. Int J Aesth Restor Surg. 1994;2:89-96.

23. Alter GJ. Correction of penoscrotal web. J Sex Med. 2007;4(4 Pt 1):844-7.

24. Perovic SV, Djordjevic ML. Penile lengthening. BJU Int. 2000;86(9):1028-33.

25. Gearhart JP et al. The Cantwell-Ransley technique for repair of epispadias. J Urol. 1992;148(3):851-4.

26. Djordjevic ML et al. Treatment for failed epispadias repair presenting in adults. J Urol. 2013;190(1):165-70.

27. Al-Ansari AA et al. Subcutaneous cod liver oil injection for penile augmentation: review of literature and report of eight cases. Urology. 2010;75(5):1181-4.

28. Lee T et al. Paraffinoma of the penis. Yonsei Med J. 1994;35(3):344-8.

29. Eandi JA et al. Penile paraffinoma: the delayed presentation. Int Urol Nephrol. 2007;39(2):553-5.

30. Orentreich DS. Liquid injectable silicone: techniques for soft tissue augmentation. Clin Plast Surg. 2000;27(4):595-612.

31. Colombo F, Casarico A. Penile enlargement. Curr Opin Urol. 2008;18(6):583-8.

32. Sasidaran R et al. Low-grade liquid silicone injections as a penile enhancement procedure: Is bigger better? Urol Ann. 2012;4(3):181-6.

33. Yacobi Y et al. Short-term results of incremental penile girth enhancement using liquid injectable silicone: words of praise for a change. Asian J Androl. 2007;9(3):408-13.

34. Panfilov DE. Augmentative phalloplasty. Aesthetic Plast Surg. 2006 30(2):183-97.

35. Kang DH et al. Efficacy and safety of penile girth enhancement by autologous fat injection for patients with thin penises. Aesthetic Plast Surg. 2012;36(4):813-8.

36. Kim MT et al. Long-Term Safety and Longevity of a Mixture of Polymethyl Methacrylate and Cross-Linked Dextran (Lipen-10®) after Penile Augmentation: Extension Study from Six to 18 Months of Follow-Up. World J Mens Health. 2015;33(3):202-8.

37. Kwak TI et al. The effects of penile girth enhancement using injectable hyaluronic acid gel, a filler. J Sex Med. 2011;8(12):3407-13.

38. Perovic S et al. Enlargement and sculpturing of a small and deformed glans. J Urol. 2003;170(4 Pt 2):1686-90.

39. Kim JJ et al. Human glans penis augmentation using injectable hyaluronic acid gel. Int J Impot Res. 2003;15(6):439-43.

40. Kwak TI et al. Long-term effects of glans penis augmentation using injectable hyaluronic acid gel for premature ejaculation. Int J Impot Res. 2008;20(4):425-8.

41. Austoni E et al. A new technique for augmentation phalloplasty: albugineal surgery with bilateral saphenous grafts--three years of experience. Eur Urol. 2002;42(3):245-53.

42. Shaeer O, Shaeer K. Penile girth augmentation using flaps "Shaeer's augmentation phalloplasty": a case report. J Sex Med. 2006;3(1):164-9.

43. Solomon MP et al. Allograft materials in phalloplasty: a comparative analysis. Ann Plast Surg. 2013;71(3):297-9.

44. Perovic SV et al. New perspectives of penile enhancement surgery: tissue engineering with biodegradable scaffolds. Eur Urol. 2006;49(1):139-47.

45. Djordjevic ML. Penile enhancement surgery. J Dtsch Dermatol Ges. 2010;8(9):645-7.

46. Bumbasirevic U et al. Hystochemical Outcomes of Tissue Remodeling after Penile Girth Enhancement Using Biodegradable Scaffolds. Urology. 2013;82(3 Supplement 1):S288.

47. Jin Z et al. Tissue engineering penoplasty with biodegradable scaffold Maxpol-T cografted autologous fibroblasts for small penis syndrome. J Androl. 2011;32(5):491-5.

PATHOGENESIS AND LABORATORY DIAGNOSIS OF CHILDHOOD URINARY TRACT INFECTION

***Jharna Mandal**

Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India
**Correspondence to drjharna@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 07.01.16 **Accepted:** 08.02.16
Citation: EMJ Urol 2016;4[1]:101-107.

ABSTRACT

Urinary tract infection (UTI) is one of the most common infections of childhood. The clinical presentations are mostly non-specific or mild. As any episode of UTI can potentially damage the kidneys, timely diagnosis and treatment are necessary to prevent renal damage. Incidence of UTI varies depending on the age, gender, and race of the child. UTIs in children are commonly caused by bacteria, though viruses, fungi, and parasites are also occasionally involved. The pathogenesis of UTI is complex where several host and pathogen factors influence the course of the disease and its outcome. Urine culture is still considered the gold standard method for the diagnosis of UTI. The means of obtaining urine samples from children for culture involves urethral catheterisation and suprapubic aspiration. The conventional methods of antibiotic susceptibility testing are labour intensive and time exhaustive. With the advent of technology, many automated platforms are available which are rapid, involve less volume of the culture or the sample, and have high accuracy.

Keywords: Pathogenesis, children, urinary tract, infections, laboratory diagnosis.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections afflicting all age groups, including children. Growing awareness has led to an increase in recognition of this disease entity and remains of immense importance, especially as it is known to present as an occult febrile illness in children, and with systemic symptoms, particularly in neonates. Despite the extensive information available, there are still some issues and challenges that need to be addressed. This article reflects on the epidemiology, pathogenesis, and laboratory diagnosis of childhood UTIs and provides a glimpse of some of the recent advancements in these aspects.

EPIDEMIOLOGY

Incidence of paediatric UTI varies depending on the age, gender, and race of the child. In the first 3 months of life, the incidence of UTI is higher in males than in females, with the male to female ratio of UTI being 2–5:1.[1] With increasing age, the incidence of UTI among females increases hugely, and the male to female ratio becomes 1:10. Reports indicate that a considerable number of children experience at least one episode of symptomatic, culture positive UTI by the age of 5 years. The prevalence of febrile UTI is higher in white infants than in black infants, with the relative risk being 6-times higher in white infants.[2] The initial presentation of UTI in children can be an occult, undiagnosed fever with or without mild gastrointestinal manifestation, or even upper and lower urinary tract symptoms.[1] It is estimated that approximately 7% of children <2 years of age present with an idiopathic fever,[2] with statistics demonstrating that the rate of febrile UTI is higher in uncircumcised boys compared with circumcised boys.[3]

AETIOLOGY

The most common causes of UTI in children are bacteria, though viruses, fungi, and parasites may

also occasionally be implicated. Adenoviruses are notoriously associated with haemorrhagic cystitis. *Candida*, on the other hand, usually cause infection in immunocompromised children. The majority (80–90%) of childhood UTIs are caused by *Escherichia coli*, followed by other members of the Enterobacteriaceae family, namely *Klebsiella*, *Proteus*, *Citrobacter*, *Serratia*, and *Enterobacter*.[4,5] Within these, *Proteus mirabilis* has an affinity towards the balanopreputial sac where it remains colonised and hence, is frequently encountered in male children. Among the Gram-positive bacterial pathogens, which are encountered less frequently compared with the Gram-negative pathogens, *Enterococcus* and *Streptococcus* (Group B usually) are commonly isolated alongside other Gram-positive cocci. As *Staphylococcus aureus* rarely causes childhood UTI, incidences could be a result of haematogenous spread. The pathogens isolated and their antimicrobial susceptibility vary depending on whether the origin of UTI is community or hospital acquired.[4,5]

PATHOGENESIS

The pathogenesis of UTI is a complex interplay of several host and pathogen factors influencing the course of the disease and its outcome. The initial step is the essential colonisation of the periurethral region by the bacteria, without which they are washed out by the force of the urinary flow.[6] The source for this is the large intestine where these organisms are present as normal commensals.[7] Female anatomy predisposes to a higher risk of developing UTI; the issue arises as the periurethral region is in relatively close proximity to the anus, and also because the urethra is shorter in females compared with that of men. Hence, the most common route of UTI at any age is the ascending route, though rare haematogenous infections are known to occur.[6]

Following colonisation, the organisms express adhesion mechanisms/factors, which are best described and evaluated using uropathogenic *E. coli* (UPEC) as an example. UPEC have fimbriae, specialised rod-like appendages that protrude from the bacterial cell surface and secrete afimbrial adhesins, such as haemolysins, cytotoxic necrotising factors, and autotransporter proteins. Amongst these fimbriae, Type 1 and P fimbriae are highly important and are more often associated with cystitis and acute pyelonephritis, respectively. Besides all these, UPEC also possess capsules and lipopolysaccharides (LPS), which protect it from the complement-mediated killing and harmful effects of the cytokines, respectively.[7] The host mounts immune defence mechanisms against uropathogens. There are a number of innate defence mechanisms that maintain the sterility of the urine within the urinary tract until the bladder neck. Beyond the bladder neck, urine can potentially be contaminated by the normal resident flora. A major defence mechanism against bacterial growth in the urinary tract is urination itself, which along with the shedding of surface epithelial cells, wards off any bacteria that may be adhered to them.[6,8,9] Therefore, any obstruction to the flow of urine may lead to compromisation of this mechanism.

A fairly common entity encountered in young males are the posterior urethral valves. These valves predispose the child to repeated episodes of UTI and vesicoureteric reflux (VUR), which in turn can lead to reflux nephropathy followed by repeated episodes of pyelonephritis and renal scarring.[10] VUR and renal scarring are more common in males than in females. Hence, extensive evaluation in males <2 years of age presenting with a UTI is required.[5,10] The bladder mucosa is well protected by a layer of mucin secreted by the transitional epithelial cells lining the bladder, and this prevents bacterial adherence. Urine itself reduces the chances of the bacteria surviving as it is acidic and has a high content of urea, other salts, and organic acids. The mucosal immune response mediated by secretory immunoglobulin A also offers some protection against the bacterial infection as it is known to bind the bacteria and prevent their attachment to the urothelium. Some endogenous products are important mediators of the innate immune defence apparatus. One such substance is the Tamm–Horsfall protein. This is secreted in the ascending limb of the loop of Henle and behaves as an immunomodulator, activating cells of the immune system, namely granulocytes and macrophages. This activation prevents the colonisation of the urothelium by uropathogens using Type 1 fimbriae.[7,8] Binding of the Type 1 fimbria activates the secretion of the other endogenous substances such as antimicrobial peptides, specifically defensins. There are two types of defensins, α and β, both of which are bactericidal. α-defensins are released by neutrophils, while β-defensins are released by the renal epithelium.[11]

Table 1: Comparison of the diagnostic tests for UTI on uncentrifuged urine.

Sensitivity and specificity	Dipstick (nitrite)	Dipstick (leukocyte esterase)	Dipstick (nitrite along with leukocyte esterase)	Microscopy (urine wet mount ≥5 WBCs/HPF)	Microscopy (Gram stain: one bacterium /oil immersion field)	Culture (semi-quantitative)	Reference
Sensitivity	50 (16–72%)	83 (64–89%)	88 (71–100%)	67 (55–88%)	93 (80–98%)	$\geq 10^5$ CFU/mL	3,12,30
	53 (15–82%)	83 (67–94%)	93 (90-100%)	73 (32–100%)	99 (99–100%)	$\geq 10^5$ CFU/mL	24,26
Specificity	98 (95–100%)	84 (71–95%)	93 (76–98%)	93 (76–98%)	79 (77–84%)	100%	3,12,30
	98 (90–100%)	78 (64–92%)	72 (58–91%)	81 (45–98%)	70 (60–92%)	100%	24,26

HPF: high power field; CFU: colony forming unit; WBC: white blood cell.

The presence of toll-like receptors (TLRs) on the epithelial lining allows them to bind to the pathogens by recognising their surface molecules. This initiates a signalling cascade, which activates an immune response. The TLRs present on the urothelium include TLR2, which can recognise the peptidoglycans in the cell wall of Gram-positive bacteria, and TLR4 which can recognise the LPS present in the cell wall of Gram-negative uropathogens.[8,12,13] Another recently identified TLR, TLR11, has a putative, but not yet established, role in the pathogenesis of UTI wherein it is said to be capable of recognising the uropathogens. In this way the latter offers protection to the kidney from bacterial damage.[14] The binding of the fimbriae to the specific TLR4 triggers a cascade of various inflammatory mediators releasing cytokines and the activation of complement.[12,13] This immune activation causes inflammatory changes leading to the recruitment of neutrophils and macrophages at the site of inflammation, and ultimately culminating in a scar formation, as well as clearing off the bacterial infection. Thus, the scar formation at sites of inflammation in the renal parenchyma is a fallout of this inflammatory cascade rather than a direct insult due to the pathogen.[12]

Circumcision is known to reduce the incidence of UTI in young males. The rate of UTIs in circumcised boys has been estimated to be around 0.2–0.4%, while the rate in uncircumcised boys has been estimated to be around 1–8%.[15] Other than age, gender, and race, the genetic composition of an individual also influences the occurrence of UTI e.g. non-secretors of the P blood group antigen are inherently at risk of developing a UTI.[16]

When given for a long time, broad-spectrum antibiotics (e.g. cephalexin, cefixime) can alter the normal microbiota present in the gastrointestinal tract and periurethral region, thereby increasing the risk of UTI. Studies have shown that when antibiotics were prophylactically given to control asymptomatic bacteriuria, the chance of UTI increased.[17] In a recent randomised, double-blind, placebo-controlled trial, RIVUR (Randomised Intervention of Children with Vesicoureteral Reflux), it was shown that antimicrobial prophylaxis among children with VUR substantially reduced the risk of recurrence of UTI, but did not reduce renal scarring.[18] The pathogenesis of UTI requires a well-coordinated and orchestrated series of all of these factors in order to begin the disease process; a better understanding of these factors is necessary for its control.

SAMPLE COLLECTION

The ideal sample for the laboratory diagnosis of UTI is urine. Urine should be collected before the initiation of antibacterial therapy, as a single antibiotic dose can be the cause of a sterile urine culture. Sampling of urine from children is a challenging task. The means of obtaining urine samples from children involves urethral catheterisation or suprapubic aspiration.[17,19-21] The sampling of urine using a collection bag or pad, though non-invasive, is unreliable as it is associated with a high contamination rate, which poses major diagnostic dilemmas. In toilet-trained children, a midstream urine sample is preferable.[2]

SAMPLE PROCESSING

Urine should be processed as soon as the sample is received in the laboratory. It is best to avoid any delay between the sample collection and

processing. Since the generation time of *E. coli* is 20 minutes, this being the most commonly implicated organism in any UTI, any delay will reflect in the culture outcome as a false significant growth, which may not be the case. In cases where a delay is expected, the sample can be refrigerated for up to 24 hours at 4°C. The use of preservatives in the sample collection vials such as boric acid (1.8%), sodium chloride-polyvinyl pyrrolidone, and boric acid-glycerol-sodium formate can reduce the problems associated with the delay met during the transportation of urine samples.[22] However, boric acid is usually associated with false negative results in dipstick testing.[23]

Macroscopic and Microscopic Examination

Macroscopic examination can provide crude indicators as to the presence of some pathologies. For example, turbid urine may indicate pyuria and red coloured urine may indicate cases of haematuria. However, these examinations are highly unreliable. Microscopic examination of urine can demonstrate the presence of pus cells, red blood cells, casts and bacteria, and yeast cells. The presence of seven or more pus cells per high power field in an uncentrifuged sample is suggestive of pyuria. On the other hand, the absence of pus cells does not reliably exclude a UTI, especially in infants <2 months of age.[24,25] It is important to note that many infants with positive urine cultures but no pyuria probably have a contamination or asymptomatic bacteriuria rather than a UTI.[26] It is now well understood that some paediatric patients with UTI can have normal urinalysis results at any given time.[2] A Gram stain of unspun urine has a sensitivity and specificity approaching 90–95%; it has several advantages as it reveals the nature of the bacterium present and therefore guides the clinician to initiate antibiotic therapy. If a single bacterium is seen under one oil immersion field in a Gram stain, it is considered to be equivalent to 100,000 CFU/mL of bacteria (Table 1).[27]

Rapid Tests for Screening

The conventional method of diagnosis by culture takes at least 24–48 hours, but rapid tests such as the dipstick test can reduce this delay. The dipstick test can detect nitrites and leukocyte esterase, and has a fairly good accuracy when compared with a semi-quantitative culture (Table 1).[28] The nitrite test detects nitrite, which is produced from the metabolism of the nitrates by Gram-negative bacteria. In the case of infection with the Gram-positive bacteria, this test will be negative as these organisms do not convert nitrate to nitrite. Hence, the likelihood of a culture being positive is high due to a Gram-negative bacterium if the nitrite test is positive. If the contact time of urine with the bladder mucosa is <3 hours, this test can be falsely negative.

The leukocyte esterase test measures presence of pus cells in urine or pyuria. This test can be falsely negative if there are a low number of pus cells. A negative dipstick test for nitrite and leukocyte esterase and no pyuria or bacteriuria on microscopic examination has a high predictive value for the urine to be sterile on culture.[27,29,30] However, this test can only be presumptive of UTI and cannot offer the antimicrobial susceptibility results, which is a major advantage with more conventional methods of diagnosis by culture.

Culture

Urine culture is the gold standard method for microbiological diagnosis of UTI.[31] The most acceptable methods of isolation of pathogenic bacteria are the pour plate method and the semi-quantitative method, the former being resource and time exhaustive. To obviate the effect of the contamination due to the commensal microbiota that colonise the periurethral meatus, the concept introduced by Kass can be applied. Kass' concept dictates that a threshold of 100,000 CFU/mL should be considered ideal for a culture to be positive in a midstream clean-catch urine sample.[32,33] This concept holds true for asymptomatic children. It is the case that 10,000 CFU/mL is considered significant in symptomatic children and even less if the child has been catheterised. Where a sample is collected via suprapubic aspiration, any number of colonies should be considered significant.[1,34,35] According to the American Academy of Pediatrics, abnormal urinanalysis (pyuria and/or bacteriuria) in the presence of 10,000 CFU/mL of a uropathogen isolated in culture is essential to establish a diagnosis of UTI.[1,26,34]

Most often UTI is monobacterial, unless there is a history of manipulation of the urogenital tract, obstruction (anatomical or otherwise) to urinary flow, or long-term catheterisation whilst receiving broad-spectrum antibiotics. It is important to distinguish true infection from contamination in cultures, and in cases where there is any uncertainty, a repeat sample should be requested. Asymptomatic bacteriuria produces a lot of

confusion in children. Long-term studies involving children with asymptomatic bacteriuria showed that the majority of them spontaneously cleared the bacteriuria without treatment and only 2–4% of these infants went on to develop a symptomatic infection. None of the school-going children developed any symptomatic UTI.[3,27,32]

Antimicrobial Susceptibility Testing

Antibiotic resistance has become a universal phenomenon among bacteria, and hence, it is the moral responsibility of all diagnostic laboratories to perform susceptibility testing on all pathogens detected. Currently, laboratories across the globe either follow the Clinical Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[36,37]

Antibiotic susceptibility testing is either performed by disc diffusion testing, by the E-strip method, with commercially available automated systems, or with platforms for minimum inhibitory concentration (MIC) detection using the Vitek® (Biomerieux), the BD Phoenix™ Automated Microbiolog (Becton Dickinson diagnostics), or the MicroScan® WalkAway® (Siemens). The advantage of these commercially available systems over the conventional methods are that they are standardised with precise, ready-to-use platforms, based on the existing guidelines of either EUCAST or the CLSI and provide rapid reports of susceptibility.

Characterisation of resistance mechanisms are of epidemiological importance. The conventional methods available to detect these are labour intensive and time exhaustive. The detection of genetic determinants of antibiotic resistance using polymerase chain reaction (PCR)-based techniques (either conventional or real-time platforms) has revolutionised the field of antibiotic susceptibility testing. These platforms provide early information on antibiotic resistance to clinicians, as they have rapid turnaround times and can be directly performed on the clinical samples.[38-40] Other methods such as the matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) and microarrays have the advantage of being even more rapid and accurate. Further to this, they can be performed on very little volume of the analyte.[41-43]

MALDI-TOF MS can detect different mechanisms of antimicrobial resistance, for instance β-lactamases, rRNA methyltranferases, etc. The spectrometer detects the peaks in the spectra generated by the hydrolysed and native unhydrolysed antibiotic molecule. The presence of a drug-hydrolysing enzyme is detected by the difference in the mass of the antibiotic molecule.[41-43] The most recent inclusion into this list of revolutionary techniques is the microfluidics-based technique, also commonly referred to as the 'laboratory on a chip'; a platform that originated from the combination of nanotechnology and bioengineering. This platform uses even smaller volumes of the analyte, which can be detected using optical, electrochemical, or magnetic devices.[38,44-46] This involves the miniaturisation of the existing benchtop PCR thermal cyclers onto a disposable microchip. The small surface and apparatus allows rapid temperature alterations in very short reagent volumes, thereby reducing the total turn-around time compared to that taken by a conventional thermal cycler. When using a microfluidic device, it is easier to monitor bacterial growth in the presence of antibiotics and determine the minimum inhibitory concentration of the antibiotics. It is also quicker, taking a few hours rather than days. Some studies have estimated the electrochemical quantification of 16S rRNA levels, membrane potential changes in response to antibiotic induced stress, or the metabolites released, to measure bacterial growth in the presence of antibiotics.[47,48]

The most advanced method for determining the origin of antibiotic resistance is next generation sequencing, by which whole genome sequencing data can be analysed using bioinformatics. This technique has not been fully utilised due to its prohibitive cost and the extensive time required to sequence and analyse the whole genome of an isolated pathogen. Once the aforementioned limitations are improved upon, this will probably be the most robust technique available to detect and map antibiotic resistance routinely.[38,49]

CONCLUSION

It is important to consider UTI in a febrile child with non-specific, vague, or mild symptoms, especially in neonates, as UTI can lead to disastrous consequences if left untended. Therefore, any single episode of culture confirmed UTI should be considered important as a potential upper UTI and thus should be treated promptly.[50]

REFERENCES

1. Grabe M et al.; European Association of Urology. Guidelines on urological infections. 2011. Accessible at: http://uroweb.org/wp-content/uploads/17_Urological-infections_LR-II.pdf. Last accessed: 7 February 2016.

2. Robinson JL et al.; Canadian Pediatric Society, Community Pediatrics Committee, Infectious Diseases and Immunization Committee. Urinary tract infection in infants and children: Diagnosis and management. Pediatr Child Health. 2014;19(6):315-19.

3. Zorc JJ et al. Diagnosis and Management of Pediatric Urinary Tract Infections. Clin Microbiol Rev. 2005;18(2):417–422.

4. Working group of the clinical practice guidelines for urinary tract infections in children. Clinical practice guideline for urinary tract infection in children. Madrid: Ministry of Health National Health Service Quality Plan, Social and Equality Policy, Aragon Health Sciences Institute;2011. pp.259.

5. Gupta P et al. Profile of urinary tract infections in paediatric patients. Indian J Med Res. 2015;141(4):473-7.

6. Mak RH, Kuo HJ. Pathogenesis of urinary tract infection: an update. Curr Opin Pediatr. 2006;18(2):148-52.

7. Spurbeck RR, Mobley HLT. "Uropathogenic Escherichia coli," Donnenberg MS (ed.), Escherichia coli: Pathotypes and Principles of Pathogenesis (2013), Amsterdam:Academic Press, pp275-304.

8. Cheasty T, Smith HR. "Escherichia," Borriello SP et al. (Eds), Topley and Wilson's Microbiology and Microbial Infections, (2005), London:Hodder & Arnold Publishers Ltd., pp. 1379-80.

9. Schulte-Wassermann H et al. Comparison of antibacterial effect of uroepithelial cells from healthy donors and children with asymptomatic bacteriuria. Eur J Pediatr. 1985;144(3):230-3.

10. Aggarwal VK, Verrier Jones K. Vesicoureteric reflux: screening of first degree relatives. Arch Dis Child. 1989;64:1538-41.

11. Ganz D. Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol. 2003;3(9):710-20.

12. Anders HJ et al. Signaling danger: toll like receptors and their potential roles in kidney disease. J Am Soc Nephrol. 2004;15(4):854-67.

13. Frendeus B et al. Escherichia coli P fimbriae utilize the toll like receptor 4 pathway for cell activation. Mol Microbiol. 2001;40(1):37-51.

14. Zhang D et al. A toll like receptor that prevents infection by uropathogenic bacteria. Science. 2004;303(5663):1522-6.

15. Singh-Grewal D et al. Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomized trials and observational studies. Arch Dis Child. 2005;90(8):853-8.

16. Cooling L. Blood Groups in Infection and Host Susceptibility. Clin Microbiol Rev. 2015;28(3):801-70.

17. Mangiarotti P et al. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. J Chemother. 2000;12(2):115-23.

18. Carpenter MA, et al. The RIVUR Trial: Profile and Baseline Clinical Associations of Children With Vesicoureteral Reflux. Pediatrics. 2013;132(1):e34–45.

19. Lau Ay et al. A comparative study of bacterial cultures of urine samples obtained by clean-void technique versus urethral catheterization. Acta Pediatr. 2007;96(3):432-6.

20. Etoubleau C et al. Moving from bag to catheter for urine collection in non-toilet trained suspected of having urinary tract infection: a paired comparison of urine cultures. J Pediatr. 2009;154(6):803-6.

21. Pollack CV Jr et al. Suprapubic bladder aspiration versus urethral catheterization in ill infants: success, efficacy and complication rates. Ann Emerg Med. 1994;23(2):225-30.

22. Gillespie T et al. The effect of specimen processing delay on borate urine preservation. J Clin Pathol 1999;52(2):95-8.

23. Delanghe J, Speeckaert M. Preanalytical requirements of urinalysis. Biochemia Medica. 2014;24(1):89-104.

24. World Health Organization. Urinary Tract Infections in Infants and Children in Developing Countries in the Context of IMCI. Discussion papers on child health. Department of Child and Adolescent Health and Development. 2005. Available at: http://apps.who.int/iris/bitstream/10665/69160/1/WHO_FCH_CAH_05.11.pdf. Last accessed: 10 February 2016.

25. Winkens RA, et al. The validity of urine examination for urinary tract infections in daily practice. Fam Pract. 1995;12(3):290-3.

26. Roberts KB; American Academy of Pediatrics, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: Clinical practice guideline for diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128(3):595-610.

27. Sobel JD, Kaye D. "Urinary tract infections," Mandell GL et al.(Eds), Mandell, Douglas, and Bennett's Principles and practice of infectious diseases (2010), Philadelphia: Elsevier/Saunders, pp. 957-85.

28. Pappas PG. Laboratory in the diagnosis and management of urinary tract infections. Med Clin North Am. 1991;75(2):313-25.

29. Mandal J et al. Utility of Urine Dipstick Test for the Screening of Urinary Tract Infection in Catheterized Women Following Gynecological Surgeries. J Obstet Gynaecol India. 2015;65(6):401-4.

30. Whiting P et al. Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr. 2005;5(1):4-17.

31. Hari P, Srivastava RN. "Urinary tract infection". Srivastava RN, Bagga A (eds.) Pediatric nephrology, 5th ed. New Delhi: Jaypee Brothers; 2011. pp.273-300.

32. Kass EH. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians 1956;69:56-64.

33. Kunin CM. A ten-year study of bacteriuria in schoolgirls: final report of bacteriologic, urologic, and epidemiologic findings. J Infect Dis. 1970;122(5):382-93.

34. Downing H et al. The diagnosis of urinary tract infections in young children (DUTY): protocol for a diagnostic and prospective observational study to derive and validate a clinical algorithm for the diagnosis of UTI in children presenting to primary care with an acute illness. BMC Infect Dis. 2012;12:158-173.

35. Health Protection Agency: Investigation of urine. National Standard Method BSOP 41 Issue 7. 2009. Available at: http://www.hpa.org.uk/srmd/div_esl_su/pdf_bacteriology.htm. Last accessed: 10 February 2016.

36. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-fifth Informational Supplement M100-S25. Accessible at: http://shop.clsi.org/c.1253739/site/Sample_pdf/M100S25_sample.pdf. Last accessed: 7 January 2016.

37. Leclercq R et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect. 2013;19(2):141-60.

38. Pulido MR et al. Progress on the development of rapid methods for antimicrobial susceptibility testing. Antimicrob Chemother. 2013;68(12):

2710-7.

39. van Belkum A, Dunne WM Jr. Next-Generation Antimicrobial Susceptibility Testing. J Clin Microbiol. 2013;51(7): 2018-24.

40. Waldeisen JR et al. A real-time PCR antibiogram for drug-resistant sepsis. PLoS One 2011;6:e28528.

41. van Belkum A et al. Biomedical mass spectrometry in today's and tomorrow's clinical microbiology laboratories. J Clin Microbiol. 2012;50:1513-7.

42. Hrabák J et al. Carbapenemase activity detection by matrix-assisted laser desorption ionization–time of flight mass spectrometry. J Clin Microbiol. 2011;49:3222-7.

43. Clark AE et al. Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry: a Fundamental Shift in the Routine Practice of Clinical Microbiology. Clin Microbiol Rev. 2013;26(3):547-603.

44. Card R et al. Evaluation of an Expanded Microarray for Detecting Antibiotic Resistance Genes in a Broad Range of Gram-Negative Bacterial Pathogens. Antimicrob Agents Chemother. 2013;57(1):458-65.

45. Kalsi S et al. Rapid and sensitive detection of antibiotic resistance on a programmable digital microfluidic platform. Lab Chip. 2015;15(14):3065-75.

46. Zanoli LM, Spoto G. Isothermal Amplification Methods for the Detection of Nucleic Acids in Microfluidic Devices. Biosensors. 2013;3(1):18-43.

47. Park S et al. Advances in Microfluidic PCR for Point-of-Care Infectious Disease Diagnostics. Biotechnol Adv. 2011;29(6):830-9.

48. Mach KE et al. A biosensor platform for rapid antimicrobial susceptibility testing directly from clinical samples. J Urol. 2011;185:148-53.

49. Torok ME, Peacock SJ. Rapid whole-genome sequencing of bacterial pathogens in the clinical microbiology laboratory—pipe dream or reality? J Antimicrob Chemother. 2012;67(10): 2307-8.

50. Vijayakumar M et al. Revised statement on management of urinary tract infections. Indian Pediatr. 2011;48(9):709-17.

Buyer's Guide

- A.M.I.
- ACCORDION MEDICAL
- ACCU-TECH CO., LTD.
- AKTORMED GMBH ROBOTIC SURGERY
- ALBYN MEDICAL
- ALLERGAN
- ALLIUM MEDICAL
- AMGEN
- ANDROMEDA MEDIZINISCHE SYSTEME GMBH
- ANGIODYNAMICS
- APOGEPHA ARZNEIMITTEL GMBH
- ASTELLAS PHARMA EUROPE LTD.
- B. BRAUN MEDICAL LTD. AESCULAP DIVISION
- BACTIGUARD
- BARD MEDICAL LTD.
- BAYER HEALTHCARE PHARMACEUTICALS, INC.
- BIOBOT SURGICAL PTE LTD.
- BIONORICA SE
- BIORAD MEDISYS PVT. LTD.
- BK ULTRASOUND
- BOSTON SCIENTIFIC INTERNATIONAL
- CARESONO TECHNOLOGY CO., LTD.
- COGENTIX MEDICAL
- COLOPLAST
- COMBAT MEDICAL LTD.
- CONCILE GMBH
- COOK MEDICAL
- CURAN MEDICAL BV
- DIREX SYSTEMS GMBH
- DORNIER MEDTECH EUROPE GMBH
- DYNAMESH BY FEG TEXTILTECHNIK MBH
- EDAP TMS
- ELMED MEDICAL SYSTEMS
- ELMEDICAL
- ELVATION MEDICAL GMBH
- EMED SP. Z O. O. SP. K.
- EMS ELECTRO MEDICAL SYSTEMS S.A.
- ENDOCARE, INC.
- ENDOCONTROL
- ERBE ELEKTROMEDIZIN GMBH
- EU-ACME
- EUROMEDICAL GMBH
- EXACT IMAGING
- EXMI TECHNOLOGY GMBH
- FERRING PHARMACEUTICALS
- GE HEALTHCARE
- GRENA LTD.
- GLAXOSMITHKLINE
- HANGZHOU BEVER MEDICAL DEVICES CO., LTD.
- HITACHI MEDICAL SYSTEMS EUROPE
- IBSA INSTITUT BIOCHIMIQUE SA
- IDL BIOTECH AB
- INTUITIVE SURGICAL
- INVIDIA MEDICAL GMBH & CO., KG
- INVIVO CORPORATION
- IPSEN
- JANSSEN PHARMACEUTICAL COMPANIES
- JENA SURGICAL GMBH
- KARL STORZ GMBH & CO. KG
- KESSEL MEDINTIM GMBH
- KLS MARTIN GROUP
- KOELIS
- LABORIE MEDICAL TECHNOLOGIES EUROPE
- LENUS PHARMA
- LILIUM OTSUKA
- LISA LASER PRODUCTS
- LP SURGICAL FIBERS/LASER PERIPHERALS
- LUMENIS
- M.A.S. MEDICAL S.R.L.
- MDXHEALTH, B.V.

Urology

- MED-FIBERS EUROPE GMBH
- MED-SONICS CORP.
- MEDA CO., LTD.
- MEDAC GMBH
- MEDI-TATE LTD.
- MEDICA S.P.A.
- MEDIELMA
- MEDIPLUS
- MEDISPEC LTD.
- MEDKONSULT MEDICAL TECHNOLOGY S.R.O.
- MEDTRONIC
- MEIKE BLADDER SCANNER
- MENARINI
- METAMARK GENETICS
- METRUM CRYOFLEX
- MIM SOFTWARE INC.
- MSD
- MTS MEDICAL
- NANOVIBRONIX LTD.
- NEOMEDIC INTERNATIONAL
- NEOTRACT
- NOVAMEDTEK
- NOVENTURE
- NUCLEIX – BLADDER EPICHECK
- NXTHERA
- OLYMPUS EUROPA SE & CO., KG
- OMEGA PHARMA
- OPTIMUM MEDICAL
- PAJUNK GMBH
- PHARMAZEUTISCHE FABRIK MONTAVIT GMBH
- PHILIPS
- PHYSION SRL
- PIERRE FABRE MÉDICAMENT
- POHL-BOSKAMP
- POLYDIAGNOST GMBH
- PROFOUND MEDICAL INC.
- PROMEDON
- PUSEN MEDICAL
- QUANTA SYSTEM SPA
- R-ACTION DISTRIBUTION
- RECORDATI S.P.A.
- RIGHTECH
- ROCAMED
- RZ MEDIZINTECHNIK GMBH
- SANDOZ INTERNATIONAL GMBH
- SANOFI
- SHENZHEN HUIKANG MEDICAL APPARATUS CO., LTD.
- SIEMENS HEALTHCARE GMBH
- SIGNOSTICS
- SOLACE THERAPEUTICS
- SONACARE MEDICAL LLC.
- SONY EUROPE LTD.
- SPECIALTY EUROPEAN PHARMA
- STORZ MEDICAL AG
- SYNERGO-MEDICAL ENTERPRISES
- SYSMEX EUROPE GMBH
- TAEWOONG MEDICAL CO., LTD.
- TEKNO-MEDICAL OPTIK-CHIRURGIE GMBH
- TELEFLEX MEDICAL GMBH
- TRISTEL SOLUTIONS LIMITED
- UROGEN PHARMA
- UROMED KURT DREWS KG
- UROMEDICA INC.
- UROVISION & UROTECH
- WATSON MEDICAL
- WELL LEAD MEDICAL CO., LTD.
- RICHARD WOLF GMBH
- YOUCARE TECHNOLOGY CO., LTD.
- ZEPHYR SURGICAL IMPLANTS