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INSIDE

Review of the
28th **EAU** Annual Congress
Milan, Italy

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Welcome

Kelly-Ann Lazarus, Editor

I am very pleased to welcome you to the first edition of *European Medical Journal - Urology*. This publication aims to provide healthcare professionals with insightful, captivating information from key opinion leaders in the field of Urology.

We are proud to present articles from revered urologists, presenting their investigations into thought-provoking, current and global issues in the field. These issues include: prostate cancer, bladder cancer, sexual dysfunctions, and urogynelogical disorders.

These articles are published alongside our independent review of the 28th European Association of Urology Annual Congress, which was held between 15th and 19th March in Milan, Italy. The Congress brought together delegates and exhibitors from all over the globe to present and discuss research and results from ground-breaking studies into the field of urology. As expected, the Congress was hugely insightful and highlights of the innovative material presented can be found in our EAU Congress Review pages within this publication.

We also provide the latest updates and most prevalent breakthroughs in scientific research and clinical practice worldwide, at the time of going to press. Featured stories report on a mobile phone application that can test urine for abnormalities, new treatment options for overactive bladder, and a discussion on PSA screening for men in their 40s.

At *European Medical Journal*, we are always seeking to improve the quality of our journals, and the information that we provide. This edition marks many of these continuous improvements, including the improvement and extension of our peer review process and also a completely new design and layout. I would like to thank our editorial board, listed opposite, a group of revered and influential professionals who assisted greatly in the quality control of this journal.

I hope that this issue becomes a useful tool for healthcare professionals by continuing to provide interesting articles and our unique, in-house congress review to further the essential sharing of research and information in the field of urology.

Kelly-Ann Lazarus, **Editor**

Foreword

Evangelos Liatsikos, M.D, Ph.D

Associate Professor of Urology

University of Patras, Greece

Dear Colleagues,

I would like to take this opportunity to introduce you to a dynamic new entry into the field of urologic publishing; the *European Medical Journal - Urology.* Aiming to publish high quality peer-reviewed articles, this journal joins the growing trend of open access in medical publishing. All articles will be freely accessible, without any charge to readers, ensuring the widest possible dissemination of valuable urological knowledge to a global readership.

The journal encourages the submission of current therapeutical developments and techniques in all aspects of urology. Clinical research, review articles, practice guides and case reports will also be featured. To safeguard the quality of the published articles, the European Medical Journal has assembled an editorial board of recognised European and American experts.

> "I am confident that colleagues around the world will quickly appreciate the quality of the material published by the *European Medical Journal*"

In addition, *European Medical Journal - Urology* reports on the most prominent urology congress with extensive coverage of this year's EAU Congress, held in Milan, Italy. Breaking news of particular interest will also be reported in the journal, and this feature is already integrated into social media platforms, providing immediately updated information to readers on their computers or mobile devices. Busy clinicians will thus be able to keep themselves informed with the latest developments in our field.

I am confident that colleagues around the world will quickly appreciate the quality of the material published by the European Medical Journal, and will soon include it in their trusted sources of information. I look forward to the development of the *European Medical Journal - Urology* into an innovative forum for the propagation of urological knowledge to readers worldwide.

Best regards,

Evangelos Liatsikos, M.D, Ph.D

Dr. Evangelos Liatsikos is currently an Associate Professor of Urology and Head of the Endourology-Laparoscopic Unit at the University of Patras, Greece. He is also a Visiting Professor in the Department of Urology of the University of Leipzig, Germany. Dr. Liatsikos' main clinical interests are laparoscopic surgery, percutaneous procedures and flexible ureterorenoscopy. In addition, he has conducted extensive research in the field of ureteral stents and the development of Laparoendoscopic Single Site Surgery (LESS).

Dr. Liatsikos has authored more than 190 peer-reviewed publications, 29 book chapters and 3 books. In 2009, he was awarded the "Arthur Award – Cook Urological" during the 27th World Congress of Endourology.

Dr. Liatsikos is a member of the European Association of Urology, American Urological Association and Hellenic Urological Association. He is an editorial board member in the *Journal of Endourology, European Urology and the International Brazilian Journal of Urology.*

EAU ANNUAL CONGRESS 2013

MILANO CONGRESSI, MILAN, ITALY

15TH - 19TH MARCH 2013

EMJ EUROPEAN MEDICAL JOURNAL

Welcome to the *European Medical Journal* review of the 28th Annual EAU Congress of Urology

EAU ANNUAL CONGRESS 2013

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WELCOME TO THE *EUROPEAN MEDICAL JOURNAL* REV UROLOGY

THE European Association of Urology (EAU) held its 28th Annual Congress in Milan, Italy between 15th and 19th March this year, marking a return to Northern Italy after the EAU first convened in Milan in 2008.

The Annual EAU Congress is a platform for the international urological community to share the latest and the most relevant knowledge with medical experts practising across the board, providing a forum for presenting original unpublished data, ideas for urological innovation and disseminating evidence-based knowledge of primary clinical relevance.

As the largest urology event in Europe, thousands of delegates and exhibitors from over 100 countries attended EAU's Annual Congress, with more than 14,000 visitors stepping through the doors of the MiCo - Milano Congressi conference centre, the largest convention centre in Europe, situated in the centre of the city of Milan.

Milan, Italy's second-largest city, is the capital of fashion, banking, and innovation, and the heartland of industry. This hardworking city of 1.3 million people was originally named Mediolanum, or "the central place", by the Romans, and by the 4th century AD, it was the capital of the western half of the Roman Empire, later becoming the city Leonardo da Vinci called home.

Today, Milan is an important centre for medical and biotechnical research, and is home to the offices of the EAU's own European Urology journal. The city is also home to centuries of impressive architecture, including the stunning gothic Milan Cathedral, the largest in the Italian state territory. The combination

of Milan's rich cultural heritage and modern infrastructure made the city a fitting location to host the Congress, this year featuring joint sessions with various international associations including the Chinese Urological Association (CUA) and Pan-African Urological Surgeons' Association (PAUSA).

This year, more than 1,200 abstracts were accepted for presentation, out of a record number of 4,172 submissions. Throughout the Congress, there were a combination of state-of-the art lectures debates, and presentations by the world's leading experts, poster

IEW OF THE 28TH ANNUAL EUROPEAN ASSOCIATION OF CONGRESS

sessions, educational activities including hands-on training, European School of Urology (ESU) courses and sponsored sessions, and live 3D surgery sessions.

The live surgeries – organised by the EAU Section of Uro-technology (ESUT) in collaboration with the EAU Robotic Urology Section (ERUS) and the EAU Section of Urolithiasis (EULIS) – transmitted both standard and 3D images to vast screens, in front of packed audiences at the Congress' main eURO Auditorium. Accompanied by commentary from surgeons and moderators, twenty cases were bought to the Section Meetings, ten live, seven pre-recorded, and three video presentations. Interest in other new technologies were also at large, as 3D flexible laparoscopy from Olympus and a video presentation on robot-assisted ureteroscopy by Turkey's Professor Remzi Saglam accompanied an exciting new imaging technology for visualising bladder tumours in SPIES-imaging from Storz.

The ethical connotations of the Congress' live surgeries were of particular focus, with follow-up information concerning last year's previous live surgery patients given before the first session, the first time it had been attempted at an event of this kind. As part of the EAU's new policy on the ethics of live surgery, it was confirmed that all organisers in the future must apply and follow the newly set out regulations in order to have the event endorsed by the EAU.

The ongoing debate regarding prostate-specific antigen (PSA) screening's benefits and harms continued throughout the Congress, mentioning topics regarding its effectiveness, the problems of limited screenings in current studies, and interestingly the need for the subject to be both open and understandable, for patients and all outside the speciality.

Accompanying the established belief that public awareness of prostate cancer has a vital role in reducing the numbers of annual deaths from the tragic condition, it was with EAU Secretary General Professor Per-Anders Abrahamsson, in reaching his presentation's conclusion, who summarised the topic best, by quoting "at the heart of the screening debate, lies the ethics of information."

FOCUS ON PROSTATE CANCER AT EAU

Prostate cancer (PCa) is the most common male malignancy in most European countries, with 346,000 new cases diagnosed each year in Europe. A major health concern in the Western male population, research efforts have increased steadily over the past two decades, and many symposiums and poster presentations focused on PCa at the EAU congress held in Milan, Italy.

Research presented at EAU included a new combination therapy for treating patients with castration resistant prostate cancer, a comparison of the comparative survival benefits of surgery to radiotherapy in men with localised prostate cancer, research on PCa risk-associated SNPs as an independent predictor of prostate biopsy outcomes, and the risk reductions of PCa diagnosis and mortality from biennial PSA screening.

PSA testing has revolutionised the diagnosis of PCa, enabling increased detection and earlier access to treatment. However, PSA measurement is not fool-proof according to Cancer Research UK statistics which have shown that around two-thirds of men with an elevated PSA level do not have prostate cancer but still suffer the anxiety, discomfort and risk of follow-up investigation. Additionally, PSA testing has a lack of specificity, as conditions other than prostate cancer, such as BPE, prostatitis and lower urinary infections, can give rise to elevated levels of PSA.

Furthermore, around 15% of men with a normal (measured as =4ng/ml) PSA level will have prostate cancer so the test can provide people with false reassurance. It is not currently possible to reliably predict which tumours will be aggressive and which will require little or no treatment.

Thus, a proportion of patients with early localised disease detected through PSA testing and then biopsy will receive unnecessary treatment with considerable side-effects. There is also a lack of consensus on the best treatment for early stage prostate cancer.

According to 2012 data from the World Health Organisation, there were an estimated 416,732 new cases of prostate cancer and 92,237 prostate cancer deaths in Europe. PCa is still one of the most common cancers to affect men and it is estimated that 1 in 5 men will develop the disease during their lifetime and three-quarters of all cases are in men aged 65 or older.

ANTIBIOTIC 'TIME BOMB' KEEPS TICKING

RISK of infectious complications after prostate biopsy highlights the significant need for antibiotics, according to Professor Florian Wagenlehner, from the Department of Urology, Pediatric Urology and Andrology Justus-Liebig-University, writing for UET Congress News.

According to a study performed on behalf of the European Section of Infection in Urology, around 5% of men suffer from symptomatic urinary tract infections (UTIs) after a transrectal prostate biopsy. This results in serious morbidity in approximately 70% of cases with systemic symptoms and re-admission into hospitals.

Professor Wagenlehner argued: "Urologists must ensure that infectious complications of biopsy do not outweigh the survival advantage of early detection and treatment. Following the introduction of transrectal ultrasound guided biopsy, this procedure has been widely accepted and optimised in recent years, continuously following the transrectal route."

With prostate biopsy performed as frequently as a million times annually in Europe alone, faecal carriage of fluoroquinolone-resistant E. coli strains are a noteworthy risk, with Professor Wagenlehner stating a single dosage treatment of antibiotics should be sufficient to treat the offending infection compared to a longer course.

"It's actually a creeping time bomb, it explodes all the time. It's not one that goes off with a very big bang at one particular moment."

- Dr. Gunnar Kahlmeter

The case for the importance of antibiotics arrives at a crucial time, with drugs increasingly losing their effectiveness, as Dr. Gunnar Kahlmeter explained in an interview with EAU: "It is actually a creeping time bomb, it explodes all the time. It's not one that goes off with a very big bang at one particular moment. There are places in the world, including Europe, where this happens every day."

However, Dr. Kahlmeter suggests there are methods to continue antibiotic efficiency: "We're trying to be wiser in the way we use antibiotics, we are trying not to squander them the way we did in the 1970s, '80s and '90s, so prudent use of antibiotics is the first thing we can do.

"The second thing we can do is we can improve our skills in preventing the spread of bacteria, and thereby also multi-resistant bacteria in our wards, in our hospitals, perhaps even in the community.

"And the third thing we can do is invent new diagnostics which will improve the speed with which we can diagnose infections, and put a name to the bacterium, and also find out whether it is susceptible or resistant to an antibiotic of our desire. And by improving that and getting that answer more quickly, we could actually wait to give antibiotics until we know what is effective."

FLAGELLIN IS KEY FOR BODY DEFENCES

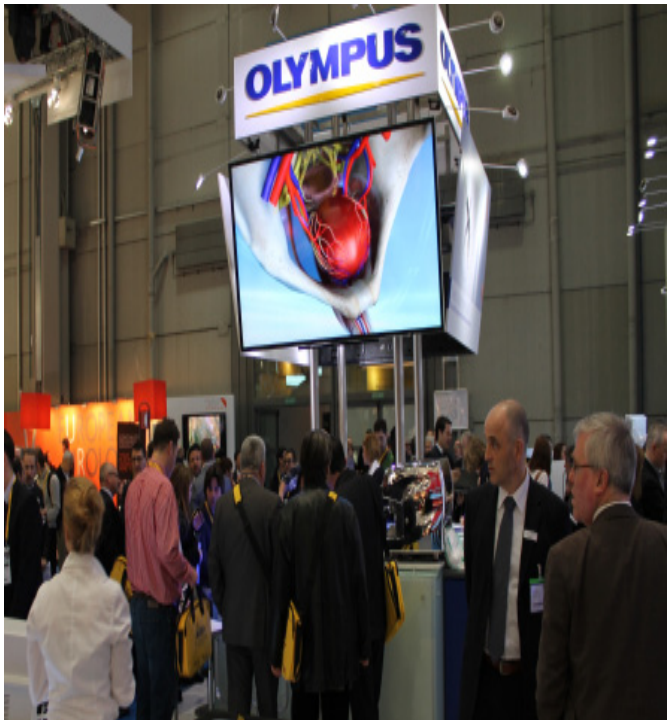
GLOBULAR protein, flagellin, was revealed to be essential in stimulating the body's natural defences, after motile Escherichia coli (E. coli) isolates were shown to activate NF-kB signalling at the 28th Annual EAU Congress in Milan on Friday 15th March.

Examining the relationship between flagellin expression and the host response, a multidisciplinary Newcastle University research team studied the motility of 24 clinical isolates associated with urinary tract infections (UTIs) and their activating NF-kB, a protein complex responsible for cytokine production and controls the transcription of DNA.

"Research into the causes and treatment of urinary tract infection is vital at this time as the incidence of UTI and bacteriuria are increasing with an ageing population," Ased Ali of Newcastle University's Institute of Cellular Medicine said while presenting the team findings.

"There is a rapidly growing resistance exhibited by organisms, especially E. coli, to conventional antimicrobials which makes infections potentially more and more difficult to treat.

"This is confounded by the fact that there have been no new classes of antibiotics to treat Gram-negative bacilli like E. coli for more than 40 years."



The study, which won the first prize award for Best Abstract for a Non-Oncology paper, continues the team's ultimate aim to develop an alternative to conventional antibiotics by developing agents that enhance the immune response and help the body defend itself better as an alternative to conventional antibiotics.

The need for an alternative continues to grow in importance, as antibiotics are often overprescribed and distributed to patients who have no bacterial infections, as well as evidence that bacteria resistance to drugs are being spread in livestock farming, due to the fact that antibiotics are a common ingredient in animal feed.

Meanwhile, in the United States, a bid to save time spent by doctors on diagnosing symptoms in the form of new website 'TreatmyUTI.com' has emerged, placing an emphasis on "safe, efficient, and cost effective" action plans for uncomplicated urinary tract infections in a bid to both increase treatments with no office visit, examination, or lab testing required.

EXTERNAL INFLUENCES HAVE POTENTIALLY KEY ROLE IN CISPLATIN-BASED CHEMOTHERAPY RESISTANCE

EPIGENETIC changes are potential key drivers in the development of chemotherapy resistance in bladder cancer, according to a study on neoadjuvant cisplatin-based chemotherapy presented at the 28th Annual EAU Congress in Milan.

DNA extracted from 48 muscular invasive bladder tumours, all with over 80% tumour content, was taken prior to platinum-based neoadjuvant chemotherapy. Neoadjuvant therapy aims to reduce the size or extent of the cancer before using radical treatment intervention, making procedures more likely to succeed, and reducing the consequences of a more extensive treatment technique that would be required if the tumour wasn't reduced in size or extent.

"Epigenetic alterations are potential key drivers in the development of chemo resistance in bladder cancer," W. Tan of the UCL Department of Surgery and Interventional Science, London, United Kingdom, wrote. "As well as providing novel insight into mechanisms of drug resistance, we have identified putative candidate biomarkers for further evaluation."

The study suggests that acquired resistance can be associated with global hypermethylation in both primary tumours and paired cell lines.

Supervised analysis determined around 2700 Methylation Variable Positions (MVPs) associated with chemotherapy response, identifying three hierarchical clusters associated with chemotherapy response: chemo sensitive, chemo resistant, and a mixed cluster with a hypomethylation phenotype.

MVPs associated with resistance include such novel genes as MEIS2, PROM1 and MAP1LC3A, plus genes previously connected to other tumour resistance, including MEST AND MLH1.

FEMALE BLADDER EXSTROPHY PATIENTS LEFT DISSATISFIED

ONLY 30% of females currently suffering from bladder exstrophy (BE) are happy with the long-term outcome of their cosmetic treatment, their concerns stemming from risks of infertility, negative body image, and urinary incontinence.

A study revealed at EAU, carried out by researchers from Kasr El Einy Hospital, Department of Urology in Giza, Cairo, followed up twenty-three female patients aged between 16-28 years old, evaluating their vulnerability, sexual function, fertility, and psychosexual dysfunction through questionnaires, paediatric medical records, and structured interviews. Twenty of the patients underwent staged primary reconstruction, while three underwent primary or secondary ureterosigmoidostomy.

"Genitourinary malformations in bladder exstrophy leads to vulnerability and psychological dysfunction and can affect all aspects of life including schooling, interactions with peers, sexuality, partnership, and fertility," the authors wrote.

The results of the study showed of the females who underwent reconstruction, three (13%) were married, two of which also having children, one after natural conception and the other through assisted reproductive technique. The remaining twenty patients were unmarried due to feelings of sexual inadequacy. Six women believed themselves unable to engage in intercourse, ten were afraid of the cosmetic appearance of their genitalia, while four suffered from incontinence. However, a research team led by Monash University and Southern Health Professor of paediatric surgery Wei Cheng, found a mutation in the P63 gene, which increases the risk of BE. Following a six-year examination of a DNA collection obtained from patients worldwide, eleven mutations were found, three associated with an increased risk of BE.

NEWLY DISCOVERED URETHRA CELLS COULD GUARD AGAINST INVADING MICROORGANISMS

A PREVIOUSLY unknown cell in the urethra of mice, called a chemosensory cholinergic brush cell, has been revealed by a recent study conducted by Ms. Katharina Filipski of the Anatomy and Cell Biology Department at Justus-Liebig-University Giessen in Germany and presented at the Congress.

These chemosensory cholinergic brush cells are in close contact to sensory neurons that express cholinergic receptors. The authors suggest that in analogy to brush cells of the respiratory and gastrointestinal tract, the urethral brush cells may also serve as sentinels being able to detect hazardous substances and prevent their further retrograde ingression.

During the study, the detection and characterisation of chemosensory brush cells of the murine urethra was addressed by means of ultrastructural immunohistochemistry, confocal laser scanning microscopy (CLSM) analysis and 3D-reconstruction, immunofluorescence, RT-PCR, and measurement of intracellular calcium concentration.

Urinary tract infections rate among the most common conditions among both out- and in-patients, and may affect all groups of populations, although elderly people and women are somewhat more likely to have them. Urinary tract infections are mainly triggered by bacteria entering the body through the urethra.

"We here have discovered a previously not recognised cell which surveils this portal of entry," said Filipski. "A further exploration of this cell population will provide insight into cellular interaction and defensive measures against pathogens."

The cholinergic chemoceptive cells may play an essential role in detecting and defending microorganisms invading the body through the urethra. The maintenance and support of their protective function could fortify the immune barrier and prevent urinary tract infections by initiating avoiding reflexes as micturition.

"It is also conceivable that dysfunction of this system might result in inappropriate urge, thereby being linked to overactive bladder," explained Filipski.

According to Filipski, the results of the study promote further research into the subject matter: "Together with the urological clinic of our university, we now aim to unravel the reflexes initiated after the detection of bacteria by the chemoceptive cholinergic cells.

"This will be addressed by cystomanometry of mice after urethral exposure to bacterial components."

URINARY STONE TREATMENTS EVOLVING INTO A NEW AGE

EMERGING new technologies are changing the face of interventional imaging, according to Dr. Cesare Marco Scoffone, Dr. Fabiola Liberale and Dr. Cecilia Maria Cracco, all of Cottolengo Hospital of Torino's Department of Urology.

The iPad and other tablet computers could have a potential role in computer-assisted surgery, as use as either a camera, a data recorder or as a guide to the patient's body throughout surgery.

Though Dr. Scoffone and colleagues point out the technology involved is both expensive and requires complicated tracking devices, a group led by Professor Jens Rassweiler have experienced iPad-assisted percutaneous access, overlapping 3D images from a 64-thin-sliced CT scan of area and surrounding

organs taken when placing the patient in the same position as on the operating table.

While biplanar fluoroscopy with a rotating C-arm has been considered indispensable since its emergence in the 1950s, fully ultrasound X-ray-free PCNL has emerged, establishing 3D shots throughout the renal puncture and therefore avoiding the risk of injuring nearby organs.

Alongside the growth in technologies concerning interventional imaging, Professor Thomas Knoll believes simple observation and the application of alpha-blockers can have an increasing role in the passing of stones.

"In terms of the urethral stones it is pretty simple, if the patient has controlled pain and you tell the patient they have a good chance the stone will pass spontaneously without any intervention, they usually go for it. And if it doesn't work, you can do the deferred treatment," Professor Knoll said.

"If the patient had no pain and they had the CAT scan for other reasons, and you tell them there is a little stone of 3mm and it might never cause any problems, for most patients it is okay.

"On the other hand, if you have patients which travel a lot or have very sensitive professions like pilots, they as for immediate treatment because if they have a colic in a foreign country or in the air, it might be difficult for them.

"It's often not only based on medical reasons but also patient preference, and if the patient likes to be safe, it is always better to do an immediate treatment. If the patient says 'Well okay, I have a 70% chance I will never have symptoms from this stone, it's okay for me.'"

PCNL TREATMENT NUMBERS RISE, DESPITE HIGH RISKS INVOLVED

PERCUTANEOUS nephrolithotomy (PCNL) use in the United States of America has risen by 47%, according to research presented at the EAU Congress 2013, with women in particular making up the majority of PCNL patients.

Data analysed included 80,097 patients who underwent PCNL from 1999-2009, during which the median age of patients grew from 51 to 55 over the decade.

Khurshid R. Ghani, MD, a urology fellow at the Vattikuti Urology Institute, Henry Ford Health System, Detroit, said: "We think this operation has become more popular in the U.S., and it's been utilised in a greater range of patients, including older patients and sicker patients."

This news comes despite the risks from such surgical intervention, with statistics supported by the National Institutes of Health highlighting complications with 30.3% of cases. Potential risks can include bleeding in and around the kidney, urinary leakage over a few days, or infection caused by bacteria trapped within the stones, although the latter is usually treated with routine antibiotics.

Carried out under general anaesthetic, PCNL removes infected or problematic stones which are damaging the kidney. Through the aid of an X-ray machine, the kidney is punctured with a fine needle through the skin, with a scope and other stone fragmentation tools such as a laser or an ultrasonic probe inserted through this tract for stone fragmentation and removal.

30.3% of cases of surgical intervention feature complications, including infection, kidney bleeding, and urinary leakage

- National Institutes of Health

DEARTH OF DATA REVEALED FOR MOST BASIC OF UROLOGICAL PROCEDURES

THERE are vast complexities associated with defining procedural competences for urological procedures, with the majority of learning curve trials focusing on the latest surgical techniques, while a dearth of data pertaining to basic urological procedures develops, according to a recent study by Dr. Hamid Abboudi and colleagues.

A learning curve describes the rate of improvement in the technical performance of a new technique over time, and is considered an important factor to consider in surgical training.

The study's objective was to determine the number of cases a urological surgeon must complete to achieve proficiency for various urological procedures. The results of this study were presented at the 28th Annual EAU Congress.

The authors systematically searched the MEDLINE®, EMBASETM®, and PsycINFO® databases until December 2011, reviewing the name of the procedure, statistical analysis, number of participants, setting of the procedure, level of participants, outcomes, and learning curves.

The learning curve for various urological procedures was defined by 49 studies. The learning curve for open radical prostatectomy ranged from 250-1000 cases, for laparoscopic radical prostatectomy from 200-750 cases, and for the learning curve for robot assisted laparoscopic prostatectomy, 40 procedures was reported as a minimum number.

Regardless of prior laparoscopic experience, there is a significant reduction noted in operative time (0.008), blood loss, (p=0.008), and complication rates (p=0.042) following 100 robot assisted laparoscopic prostatectomies.

The learning curve for robot assisted radical cystectomy was reported to range from 16-30 cases, depending on which outcome variable is being measured.

Meanwhile, converting from laparoscopic to robot assisted partial nephrectomy would require a LC of 5–25 cases.

The authors emphasised that the available literature can act as a guide for the learning curve of trainee urologists and while the learning curve may vary amongst individual surgeons, a consensus should exist for a minimal number of cases to achieve proficiency.

Authors explained: available literature can act as a guide for the learning curve of trainee urologists

CALL TO IMPROV

PATIENTS' dissatisfaction over current treatment options for male infertility, ejaculatory, and erectile dysfunction is adding to calls for new drugs to treat these andrological conditions.

The developing of new, superior drugs with novel properties that may help patients currently unhappy with treatment options falls into the prevalent and topical discussion of personalised medicine, that has resonated across urology, and many of its subspecialties, throughout the EAU conference.

Personalised medicine has been discussed at the meeting of the EAU Section of Urolithiasis (EULIS) which focused on a personalised medicine approach to the management of kidney stones. Additionally, Prof. Hein Van Poppel delivered a presentation on the question of "To Treat or not to Treat Small Renal Masses", arguing treating such masses is "very much a case of personalised medicine".

"Andrology is one of the fields where personalised medicine is a more sensitive topic," said Dr. Ferdinando Fusco, of University Hospital Federico II, Italy. "The personal feelings of the patient are much more important than any objective measure."

Fusco spoke of the use of aromatase inhibitors (AIs), a drug

VE TREATMENTS FOR ANDROLOGY

usually used in treatment of breast cancer, to increase the testosterone to estragon ratio, sperm number and sperm motility in patients with a lower testosterone to estragon ratio and idiopathic infertility. This finding links infertility to metabolic syndrome.

He then commented on the current needs for further advancement in the field, saying "Many drugs available can palliate the symptom, can treat erectile dysfunction, as long as you take the drug, but the thorough need to many patients is something that can rehabilitate them to a spontaneous and happy sexual life."

Additionally, Dr Andrea Salonia, during his state-of-the-art lecture title 'Modern management of ejaculatory disorders', argued that premature ejaculation (PE) treatment is not well-outlined. He argued that this was due to underdiagnosis in clinical practice, a lack of adherence to the treatment guidelines from urologists, a lack of a widely recognised 'gold standard' treatment, as well as a host of side effects which are characteristic of almost all of the compounds available for PE. This has led to off-label daily dosing of drugs such as a paroxetine and fluoxetine.

Recently, however, dapoxetine hydrochloride, a short-acting serotonin-specific reuptake inhibitor (SSRI) with a pharmacokinetic profile that is favourable for on-demand treatment of PE, has been launched as the first on-demand and on-label treatment for PE.

"Androlology is one of the fields where personalised medicine is a more sensitive topic...The personal feelings of the patient are much more important than any objective measure."

- Dr. Ferdinando Fusco

STEM CELLS MAY PROVIDE NOVEL ERECTILE THERAPY

A STUDY has shown that transplantation of mesenchymal stem cells cultivated on the surface of nanofibrous meshes (nano-human mesenchymal stem cells) could be a novel therapeutic strategy against post-prostatectomy erectile dysfunction (ED). The study, conducted by Prof. Y.S. Song of Soonchunhyang University School of Medicine in South Korea and colleagues, was awarded 3rd prize for best abstract in non-oncology research on the opening day of the congress.

The objective of the study was to examine the differentiation of human mesenchuymal stem cells cultivated on the surface of nanofigrous meshes into neuron-like cells and repair of ED using their transplantation around the injured cavernous nerve (CN) of rats.

Treatment of phosphodiesterase five inhibitors provides limited effectiveness in the treatment of post-prostatectomy ED and it is believed that the transplantation of stem cells cultivated on the surface of nanofibrous meshes can promote cavernous neuronal regeneration and repair ED.

Over the course of the study, the synthesised polymer was electrospun in a rotating drum to prepare nanofibrous meshes and human mesenchymal stem cells (hMSCs) were prepared and confirmed. Eight week old male Sprague-Dawley rats were divided into four groups of ten each, including sham operation (group 1), CN injury (group 2), hMSCs treatment after CN injury (group 3), and nano-hMSCs treatment after CN injury (group 4).

Immediately after the CN injury in group 4, nano-hMSCs encircled the injured CN. Erectile response was assessed by CN stimulation at two and four weeks. Subsequently, penile tissue samples were harvested and examined using morphological analysis and immunohistochemical stain against nerves (nestin, tubulin βIII and map2), endothelium (cluster of differentiation 31, von Willebrand factor) and smooth muscle (smooth muscle actin).

> Around 30% of men who take sexual performance enhancing drugs see no improvements
>
> - Sexual Advice Association

The results of the study revealed that at two and four weeks, transplantation of nano-hMSCs increased the expression levels of cavernous neuronal, endothelial and smooth muscle makers more than hMSCs alone.

Additionally, nano-hMSCs increased the neuronal differentiation of mesenchymal stem cells more than hMSCs alone, and the mean percent collagen area of caversnosum increased following CN injury and recovered after transplantation of nano-hMSCs more than hMSCs alone.

Furthermore, the group with CN injury had significantly lower erectile function than the group without CN injury ($p<0.05$). The group transplanted with hMSCs showed higher erectile function than the sham operation group ($p<0.05$), whereas the group transplanted with nano-hMSCs showed higher erectile function than the group with hMSCs alone ($p<0.05$).

The authors of the study concluded that nano-hMSCs differentiated into neuron-like cells and their transplantation repaired ED in the rats with CN injury. These findings have high potential for the development of follow-up research projects.

"The outcomes of the current study could be a starting point for investigating clinical application of autologous adipocyte derived mesenchymal stem cells cultivated on the nonofiber to the injured caverneous nerve after radical prostatectomy," said Song. "This is necessary to evaluate the effectiveness and safety of transplantated human mesenchymal stem cells cultivated on the surface of nanofibrous meshes against post-prostatectomy erectile dysfunction in patients with cavernous nerve injury."

NOCTURIA CAUSES 25% LOWER WORK PRODUCTIVITY

PEOPLE suffering from nocturia are nearly 25% less productive at work, making it as disadvantageous as other common chronic disorders such as asthma.

The study also reveals the condition – where individuals are forced to wake up during the night to urinate – means a third of all sufferers are unable to go back to sleep after waking, leading to disturbed sleep and insomnia.

Philip Van Berrebroeck, MD, PhD, of the University of Maastricht, said: "Nocturia is a common problem affecting around one-third of adults, but its burden is underestimated and it is often dismissed as being less serious than other chronic conditions in terms of impact on quality of life and societal costs."

The work productivity loss of 24% efficiency is higher than the 10-12% from sufferers of overactive bladder, while additional research suggesting this loss of productivity costs European businesses around €3,700 per patient annually.

Other data presented at the EAU Congress found people

considered the worst of all symptoms to be fragmented sleep, according to an analysis of subjective, patient-reported data taken from two randomised controlled trials involving 273 women and 513 men.

One patient explaining her frustration said: "I can't ever fall back asleep. I start watching TV all night and I am miserable the next morning."

This tiredness can lead to an increased risk of falling accidents, affecting the elderly in particular. Those suffering from nocturia see their risk of falling rise from 10% to 21% by visiting the toilet three or more times nightly over the course of the year.

The best therapy for nocturia is widely accepted to be desmopressin, a synthetic version of the bodily hormone vasopressin which regulates the body's retention of water. With the treatment deemed superior to placebo, the European Association of Urology guidelines outline that desmopressin is well-tolerated, and results in significant improvements.

Sleeping less than five hours per night on average reduces your life expectancy by 15%

- National Health Service

Burden of Illness and Optimal Management of Recurrent Cystitis

Summary of Presentations given at the OM Pharma Symposium 28th Annual EAU Congress, 15-19 March 2013

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Antimicrobial Susceptibility and Resistance in Urological Infections Worldwide: Surveillance and Prevention

Florian ME Wagenlehner

Antimicrobial resistance in urological infections and antibiotic resistance in general is a worldwide problem. There is known antimicrobial resistance in healthcare associated (nosocomial) infections. In addition to the nosocomial antimicrobial resistance, there is increasing evidence that there is growing antimicrobial resistance in community-acquired infections. The reason for this increase is antibiotic consumption; the antibiotic consumption in Europe is 10,500 tons each year, 52% is for human use and 48% is for animal use. 80% of the human use is in the outpatient setting.[1,2] There is a significant difference in geographical distribution regarding antibiotic consumption. The total antibiotic consumption worldwide, classified in defined daily doses (DDD), is much lower in northern countries than southern countries.[3] Furthermore, the total antibiotic consumption in the community strictly correlates with increasing antimicrobial resistance, which eventually leads to multi-antibiotic resistance.[4] Therefore, antibiotic resistance is a significant threat to human health as identified by the WHO. In Europe 25,000 patients a year die from multi-drug resistant bacteria. This equates to more deaths than in HIV/AIDS, Parkinson's disease, emphysema, and homicide and results in healthcare costs of more than 1.5 billion euro per year.[5]

Cystitis is a benign condition but it is one of the most common forms of urinary tract infection (UTI). In addition, UTI is one of the most frequent forms of infection in general, and recurs frequently in about a quarter of women. Cystitis accounts for a large percentage of the antibiotics given to patients; although it is not a life threatening condition, it has a large impact on antibiotic consumption. Since antibiotics, in particular against uropathogens, are limited and resistance rates in the community are increasing, new antimicrobial substances that have an exclusive indication for cystitis are warranted.[6,7,8,9]

According to several surveillance studies, the main pathogen involved in uncomplicated cystitis is *Escherichia coli* (*E. coli*). The ECO-SENS study[4] in Europe and Canada found that in acute uncomplicated cystitis in 2003 and 2011, 77% and 74% (respectively) of isolated pathogens present were *E. coli*; correspondingly the ARESC study in Europe and Brazil found that 76% of the pathogens present were *E. coli*.[10] The NAUTICA study,[11] which was a microbiological study of outpatients, found 58% of the pathogens were *E. coli*; this result was lower than other surveillance studies because the study population included patients with complicated UTI. The surveillance studies also investigated the total spectrum of antibiotic resistance. The largest resistance shown in all 3 studies was to ampicillin, followed by trimethoprim/sulfamethoxazole (TMP/SMX) which is one of the standard treatments for uncomplicated cystitis. Fluoroquinolones have a slightly lower resistance rate, but resistance to this antibiotic

ECO.SENS – 2003/11 N.-Europe, Canada	NAUTICA – 2006 USA, Canada	ARESC – 2008 Europe, Brazil
SRGA standard	CLSI standard	CLSI standard
Ampicillin – 26/28%	Ampicillin – 38%	Ampicillin – 51%
TMP/SMX – 13/17%	TMP/SMX – 21%	TMP/SMX – 29%
Nalidixic acid – 4/10% Ciprofloxacin – 1/4%	Nalidixic acid – n.d. Ciprofloxacin – 5%	Nalidixic acid – 18% Ciprofloxacin – 8%
Nitrofurantoin – 1/0.3% Mecillinam – 2/1% Fosfomycin – 0.4/1%	Nitrofurantoin – 1% Mecillinam – n.d. Fosfomycin – n.d.	Nitrofurantoin – 5% Mecillinam – 3% Fosfomycin – 1%

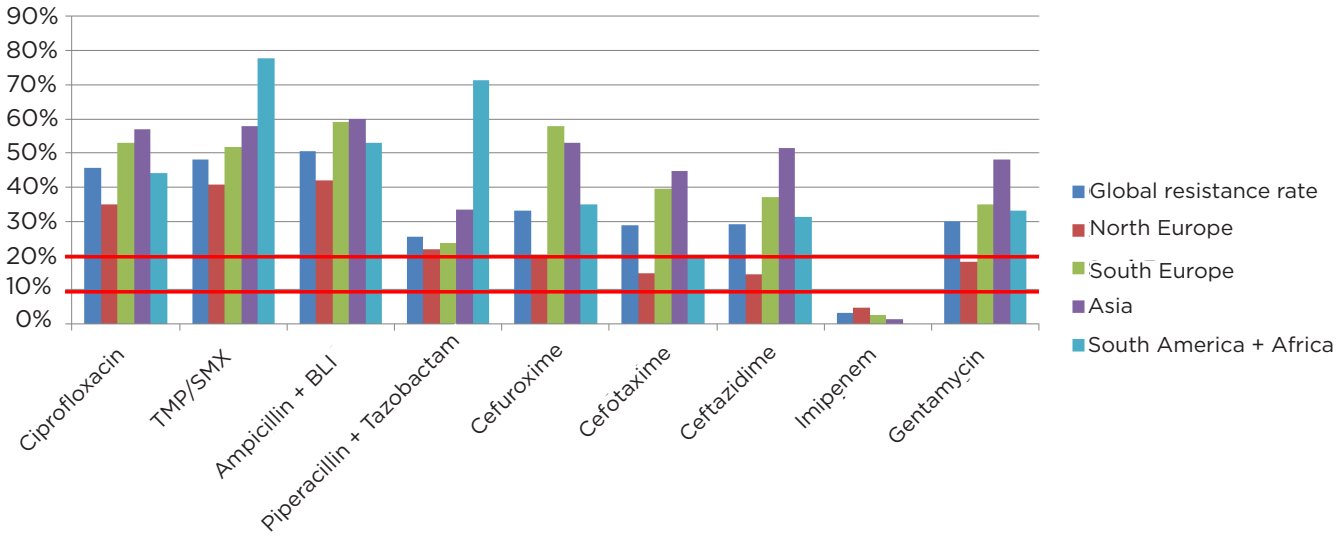
Figure 1. Surveillance studies on *E.coli* antimicrobial resistance

class has increased significantly in the last years.(Figure 1)

In some countries resistance rates for antibiotics used in uncomplicated cystitis are very high for example in South-Korea where 73% of pathogens were resistant to ampicillin.[12] The Global Prevalence study of Infections in Urology (GPIU)[13] investigated nosocomial-associated urological infections. The study database included approximately 20,000 patients and almost 2,000 (9.4%) of patients had a nosocomial-acquired urinary tract infection (NAUTI). The study confirmed that the spectrum of uropathogens in hospitalised urological patients who have complicated UTI differs from those of uncomplicated UTI and that *E. coli*, which accounts for 75–80% of infections in uncomplicated UTI, is responsible for only 40%[14] of complicated UTI. The remaining infections are caused by other pathogens such as *Citrobacter spp* and *Pseudomonas aeruginosa*. In NAUTI, the global *E. coli* resistance rates to antimicrobials are considerable: for example resistance to fluoroquinolones is 40%, although there are some differences between regions. Therefore, if antibiotics are to be used empirically for severe infections (as any treatment delay can be fatal) only antibiotics with a low resistance threshold level (lower than 10%) should be used. This is because treatment with an inadequate antibiotic in the first instance can also lead to an increased mortality rate. (Figure 2)

Nowadays for an effective treatment of severe infections such as urosepsis, globally only carbapenems would meet the required low resistance threshold level. For more benign conditions such as uncomplicated UTI, a higher resistance rate (a threshold of 20%) is more acceptable. Antibiotics with a threshold of more than 20% are not recommended as first-line empirical treatment. Unfortunately very few antibiotics meet this threshold level. The extensive use of cephalosporins has led to positive selecting pressures for Gram-negative organisms that produce Extended Spectrum Beta-Lactamase (ESBL). In geographical areas such as India[15] some ESBL *E. coli* strains have shown extremely high rates of antibiotic resistance and this is a global trend. The SMART study[16]

Figure 2. Global and regional resistance rates of *E.coli* in GPIU study



investigated multi-resistant organisms and found that the incidence of ESBL-producing strains has increased dramatically - particularly in Asia and Latin America.

Likewise in Europe there are significant rates of ESBL-forming bacteria. ESBL forming bacteria are not only resistant to penicillins and cephalosporins, but have a core resistance to other antimicrobials; 40% are resistant to ciprofloxacin and 90% are resistant to amikacin (an antibiotic from the aminoglycoside class that has a very restricted use in the patient population). The observed frequent core resistance translates into increased mortality rates. A patient infected with ESBL-producing organisms has increased mortality[17] compared with a patient who is not infected with such pathogens. This is because there is a paucity of effective antibiotics.

As the prevalence of bacteria producing ESBL increases, progressively more broad-spectrum antibiotics, such as carbapenems, will become the last resource available to treat severe infection. Furthermore, as the use of carbapenems increases, more carbapenem-resistant strains will develop; there are some candidate bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter sp.* that already contain genes conferring resistance to carbapenems. This has been illustrated by the New Delhi Metallo-β-lactamase 1 (NDM-1) gene; the gene has been transported from India[18] into Europe and has been found in bacteria causing UTI in patients. Due to the high mobility of the population, NDM-1 has spread quickly throughout the world. The NDM-1 gene confers resistance not only to carbapenems, but also to almost all antibiotics that are available.[19] Now only older and very toxic antibiotics such as colistin have become candidates to treat such infections. These antibiotics were not used previously due to their high toxicity profile; all other available 'reserve' antibiotics have been found to have high rates of resistance among bacteria.

We are approaching a post-antibiotic era; there are no antibiotics currently available for the treatment of multi-resistant strains. In the past, the resistance issue was managed by the development of new antibiotics (between 1983 and 1987, 16 new antibiotics were approved); in recent years the scenario has changed and only one new antibiotic was approved between 2008 and 2009.[20] Furthermore, there are no new antibiotics in the pipeline for use against multi-resistant bacteria, although there are some new compounds that facilitate the effect of older compounds (e.g. the beta-lactamase inhibitor avibactam).[21]

An added consideration in antibiotic use is 'collateral damage', which occurs when a patient is given a systemic antibiotic. The systemic antibiotic targets not only the bacteria that are causing the infection but symbiotic microflora as well. Third-generation cephalosporins, fluoroquinolones and carbapenems have a detrimental effect on the normal microflora, and the more broad-spectrum the antibiotic is, the higher the collateral damage.

With insufficient new antibiotics in the pipeline the only option is the prudent and judicious use of existing antibiotics.[22] This requires careful consideration of the indication, the antibiotic safety profile and resistance rate and the consideration of other strategies such as prophylaxis. This approach to antibiotic use is termed 'antibiotic stewardship', a multi-factorial strategy comprising a variety of individual approaches such as infection prevention and control, vaccine or immunotherapy, improved diagnostics to enable resistant bacteria to be more readily recognised, reduction of 'resistant reservoirs' (e.g. catheters), production of benchmarks and education.

In conclusion, antibiotic resistance is important both in the hospital and the community. Antibiotic resistance, especially in Gram-negative pathogens, represents a significant threat to clinical urology in the management of UTI. Alternative strategies to the use of antibiotics for treatment and strategies for prevention must be implemented in order to cope with this urgent and alarming situation. Antibiotic resistance is an increasing and dramatic problem. Therefore, for the optimal management of recurrent cystitis, several guidelines recommend alternative preventative approaches (with different recommendation grades) such as immunotherapy, vaginal probiotics and phytotherapy.[23]

Guideline in Urinary Tract Infections: The Place of Immunoactive-Prophylaxis in Recurrent UTI Management

Kurt G. Naber

Recurrent UTI (rUTI) are common among young, healthy women with anatomically and physiologically normal urinary tracts (Level of Evidence 2a).[23] Recurrent uncomplicated UTI (cystitis) is defined as at least 2 acute documented infections (with at least 2 clinical symptoms, no vaginal discharge/irritation and positive urine culture) in 6 months or at least 3 acute documented infections in 1 year.[24]

40% of women will experience UTI in their lifetime[6] and about 25% of them will experience another episode within 6 to 12 months. rUTI is a genuine burden for women and between 4 and 10% will suffer from rUTI.[7] Antibiotic treatment of the acute UTI episodes is not sufficient to relieve this burden and an effective prevention strategy is urgently needed.[8]

The management of rUTI is clearly stated in the EAU guidelines[23]: The acute episode should be treated with short-term antibiotic therapy and then the recurrences managed with prophylaxis.

Cystitis is a benign but aggravating condition; the pain and discomfort experienced cause both inconvenience and disturbance of daily life. Women also experience anxiety due to the sudden, painful new infection, and are often forced to change their daily plans (known as avoidance behaviour) when they are suffering from recurrent cystitis.[24] The aim of prophylaxis is to improve the quality of life of the patient by reducing the recurrences, and to avoid antibiotic side effects, to reduce the evolution of resistance and to preserve host flora by using antibiotics sparingly.

Nitrofurantoin can be used for UTI prophylaxis, however rare but serious hepatic and pulmonary side effects have been observed. In France the use of nitrofurantoin is contraindicated for prophylaxis of recurrent treatment of UTI.[25] The use of antibiotics in the treatment of UTI represents a vicious cycle[26] due to the 'collateral damage' of the host microbiota. (Figure 3)

The current guidelines for the management of rUTI[24,27,28,29] state that prevention of UTI should be promoted and that antimicrobials should be avoided. Approaches to prevention of rUTI are: behavioural modification (which is not always feasible), non-antimicrobial prophylaxis and antimicrobial prophylaxis.[23,30] The therapeutic options recommended in the EAU guidelines (last updated 2013)[23] are to consider general prophylaxis initially, i.e. counselling and behavioural modification; secondly, consider non-antimicrobial prevention (in order to spare antibiotics); and finally, to consider antimicrobial prevention only when non-antimicrobials have been unsuccessful (Level of Evidence 2b, Grade A).

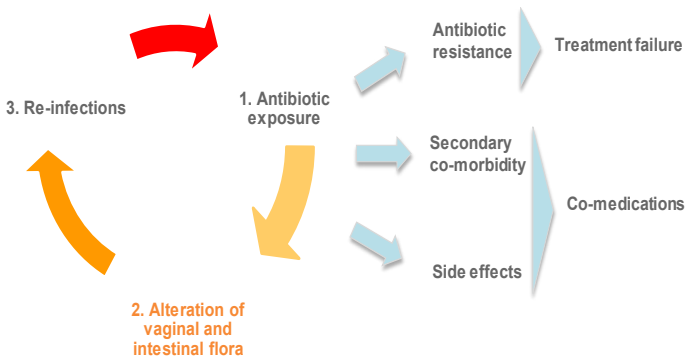
If antimicrobial prophylaxis for recurrent cystitis is required, the most recent EAU guidelines[23] recommend antibiotic use daily or after intercourse, and specify the doses to be used. There are no recent studies on the use of antimicrobial prophylaxis in the treatment of UTI, therefore very old studies must be used, that often no longer take into account bacterial resistance rate.

The EAU guidelines[23] recommend the following non-antimicrobial prophylaxis treatments; each is given a level of evidence grade (LE) and a recommendation grade (G). A recommendation Grade A represents 'you must', Grade B represents 'you should', Grade C represents 'you can' and Grade D represents 'we do not know/ we cannot recommend'.

The use of oestrogens (especially vaginal) in post-menopausal women with rUTI have been shown to be effective[31] but results are contradictory (LE: 1b; G: C). Probiotics (in which the specific *Lactobacillus sp*. strain has been tested) should be used for prophylaxis. Intravaginal probiotics that contain *L. rhamnousus GR-1* and *L. reuteri RC-14* should be used for the prevention of UTI; these products can be used once or twice weekly (LE: 4 G: C). Oral probiotic products containing *L. rhamnousus GR-1* and *L. reuteri RC-14* can restore the vaginal lactobacilli, compete with urogenital pathogens, and prevent bacterial vaginosis, a condition that increases the risk of rUTI (LE: 1b G: C). There is some evidence that cranberry (*Vaccinum macrocarpon*) is useful in reducing the rate of lower UTI in women (LE: 1b G: C). So a daily consumption of cranberry products, giving a minimum of 36 mg a day of proanthocyanidin (the active compound) is recommended (LE: 1b G: C); it is noted that only those compounds that have demonstrated clear bioactivity in the urine should be used. However, a Cochrane review[32] of 24 studies that included 4,473 participants found that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall (RR: 0.86%; CI: 95% [0.71 to 1.04]).

Oral immune-prophylaxis with OM-89, made from lysates of several strains of *E. coli* that stimulate mainly but not

Figure 3. Breaking antibiotic's vicious cycle



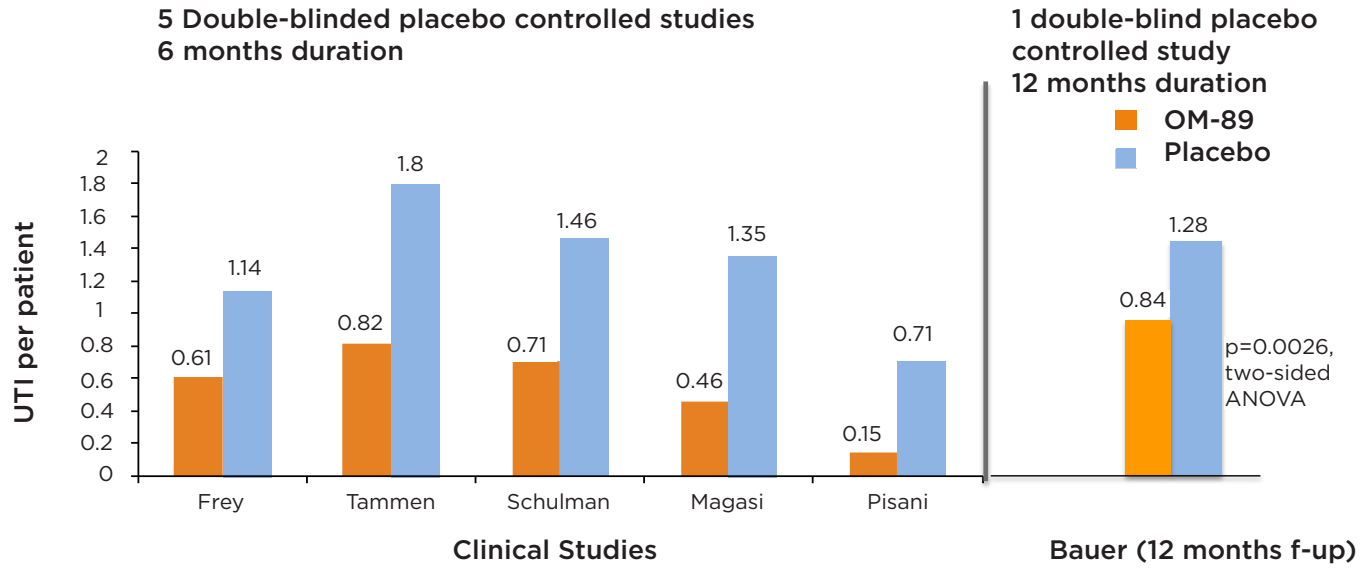


Figure 4. Results from OM-89 double blind placebo controlled trials

exclusively the innate immune system of the urinary tract, is sufficiently well-documented and has been shown to be more effective than placebo in several randomised trials[33,34,35,36,37,38] all showing a reduction of approximately 30-50% in UTI episodes. (Figure 4)

With a Level of Evidence (LE) 1a and a recommendation of use, Grade (G) B OM-89 is therefore recommended by the EAU guidelines and should be used in female patients with recurrent uncomplicated UTI. OM-89 has also been recommended by the Brazilian Medical Association since 2010, and in the Russian National Guidelines 2012.

Many patients suffer from rUTI and there are several strategies for the prophylactic treatment of these patients. The EAU Guidelines[23] describe the management of rUTI and make recommendations on the prophylactic measures available. The clear message is that only a few antibiotics are suitable for antimicrobial prophylaxis due to the problems of resistance, compliance, and adverse events, and they should only be used as a last resort.

The Burden of Illness of Recurrent UTI: Clinical Benefit of Oral Immunostimulation and Impact on Patients' Quality of Life

Björn Wullt

The impact of UTI can be measured in alternative ways; e.g by antibiotic consumption, its subsequent 'collateral damage' and the increasing microbial resistance in society. UTI has also a considerable economic cost and it is a major cause of sick-leave and morbidity. Consequently, the effect of UTI can be measured by its impact on quality of life (QoL).[39] It is generally considered that UTI has an impact on QoL, but this has previously been unsupported by data.

OM-89 is an extract from 18 uropathogenic *Escherichia coli* (UPEC) strains that is administered orally. Awareness of the mode of action of host defences is essential in understanding the mechanism of action of OM-89. There are two lines of host defence: native immunity (defence line 1) has two functions. The first function is as a physical barrier comprising the uroepithelium and the urinary flow combined with the regular and ideally complete bladder emptying, removing the bulk of possible bacterial growth. This function does not need an antigen, it is innate. The second part of native immunity is non-adaptive inflammation and the recruitment of neutrophils via Pathogens Associated Molecular Patterns (PAMPs) recognition. This is mainly mediated by Pattern Recognition Receptors (PRRS), mainly Toll-like receptors on the mucosal cells. Native immunity is a fast defence mechanism.

Adaptive or specific immunity (defence line 2) is a slow defence; antigens and antigen presenting cells are required, and there is a need for repetitive antigen challenge. Very briefly described, exogenic antigens are engulfed by dendritic cells that transmigrate to lymph-nodes in which circulating T- and B-cells are activated. By homing, activated T-cells and antibody producing B-cells, return to the place of the primary antigen exposition. This adaptive immunity works in 'compartments', e.g. the Gut-Associated Lymphoid Tissue (GALT) and Mucosa-Associated Lymphoid Tissue (MALT).

In the urinary tract, bacteria come into contact with the

uroepithelial lining and the Toll-like receptors are activated by antigens patterns recognition with or without fimbriae attachments; pro-inflammatory genes are activated in the uroepithelial cells and cytokines are secreted into the urine causing neutrophils to be recruited. This initiates the inflammatory cascade.

Immunoglobulins can also be measured in the urine, but their protective role is unclear. In experimental animal models, adaptive immunity can be 'knocked out', without effect on the clearance of acute UTI. Therefore, the importance of adaptive immunity is probably relative in acute UTI. In contrast, native immunity is crucial for an intact host defence in acute UTI.

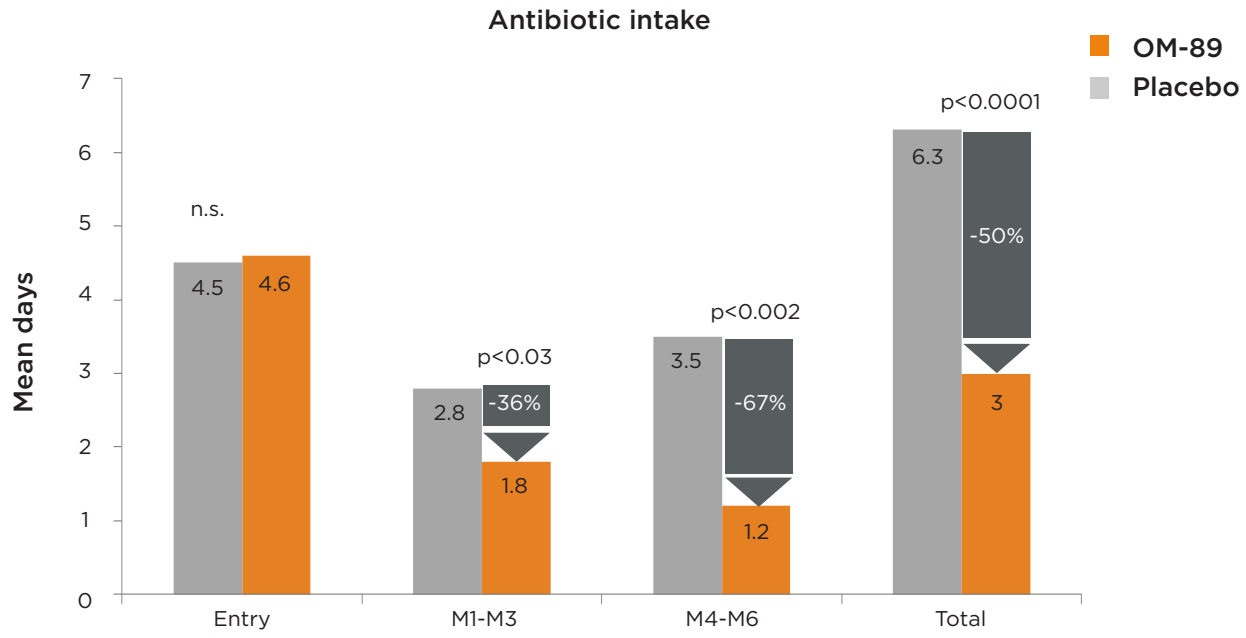
The limited protective effect of adaptive immunity in acute UTI is of course a major obstacle in vaccine development. In addition, UPEC consists of thousands of different strains and it is therefore not possible to produce only one antigen to use as an effective vaccine candidate. Efforts have been made to make a vaccine from common bacterial properties as the adhesion of the type 1 fimbriae or iron uptake receptors, but they have as yet been unsuccessful. An alternative approach is to use several antigens. OM-89 is an example of this as 18 UPECs extracts are included in the compound. There are few other products of this type available and those that are have different modes of administration.

Experimental studies support the concept that OM-89 can stimulate the immune system at urinary tract level. In laboratory studies it has been shown that OM-89 stimulates innate immunity via the macrophages and dendritic cells,[40] and it has also been shown to cause T and B cell activation which are essential elements of specific immunity.[40,41] Reduction of bladder inflammation has been observed in mice fed with OM-89 orally; the study showed that OM-89 had a protective effect in the urinary tract from lipopolysaccharide induced inflammation in the bladder.[42]

The clinical efficacy of OM-89 has been shown in several placebo controlled trials from 6 months' (5 double-blind placebo controlled trials)[35,42,44] to 12 months' duration (1 double-blind placebo controlled trial).[43] All of the studies have shown a significant reduction in the recurrence rate of UTI of between 30 and 50%. The Schulman study[37] showed that OM-89 reduced the number of UTI recurrences by 49%, which was statistically significant ($p<0.001$). In addition, there was a correspondingly highly statistically significant antibiotic sparing effect in the patients treated with OM-89 compared with the placebo group (50%, $p<0.0001$, chi-square test). (Figure 5)

The Bauer study[35] showed that after 12 months, the mean rate of UTI was significantly reduced by 34% in the OM-89 group compared with the placebo group ($p<0.003$). Furthermore, there were a larger proportion of females (20%) without any recurrence during the study period compared with placebo treated patients. In the Naber meta-analysis,[43] data from all main clinical studies that had

Figure 5. Significant antibiotic consumption reduction in OM-89 group over a 6-month period



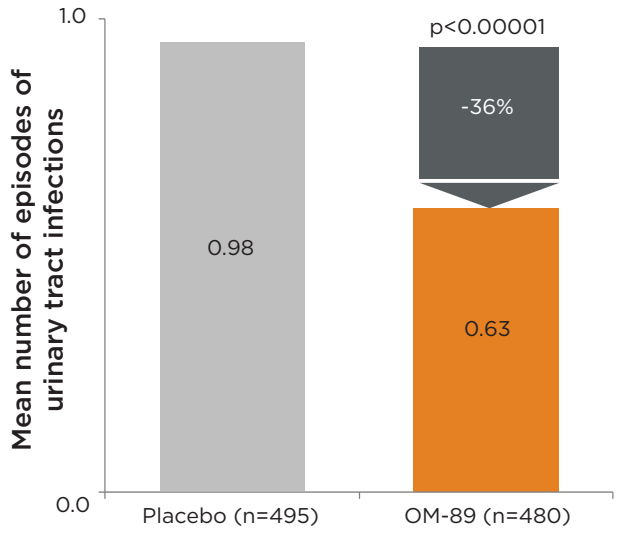


Figure 6. Significant reduction of mean number of UTI in OM-89 group over a 6-month period

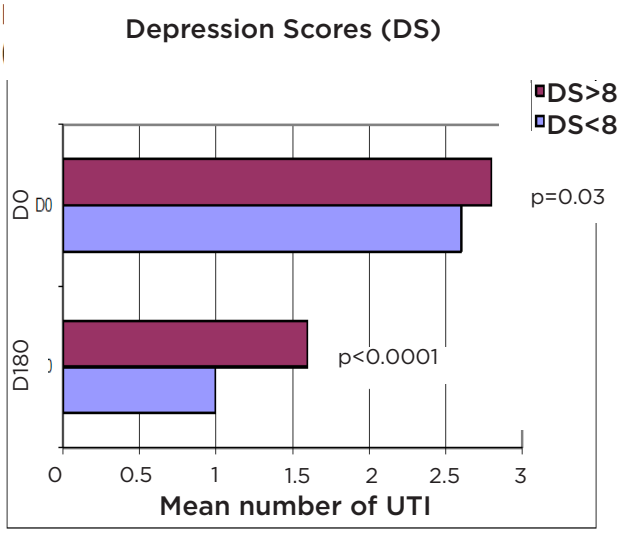


Figure 7. Number of urinary infections and depression score at Days 0 and 180 - overall (N=575)

been performed were reviewed and the analysis found a 36% reduction in the mean number of UTI after 6 months in the OM-89 treated population compared with the placebo population. (Figure 6)

There has been a complete lack of data on QoL in patients with rUTI. A recent international, prospective, observational, multicentre survey[44] evaluated 575 patients who had UTI episodes in the last 12 months for whom preventative treatment using long-term medication was planned. The patients were given optimal prophylaxis according to Best Standard of Care, including OM-89 (94% of patients). To measure QoL, 2 self-assessment questionnaires were used, the Hospital Anxiety and Depression scale (HAD) and the Leicester Impact scale. The HAD scale measured depression and anxiety and the Leicester Impact scale assessed social or functional handicap to determine the impact of urinary problems on daily activities, mood and behaviour. The endpoints were the QoL indicators at inclusion and at 6 months (Day 0 and Day 180). At baseline, 62% of patients presented with a global HAD score indicative of minor depression or anxiety (74% of patients exhibited anxiety symptoms and 36% showed depressive symptoms). The Leicester Impact score showed that 74% of patients suffered from disturbance of their daily activities. These baseline data indicated that patients with rUTI experienced impaired QoL; therefore it was investigated if this was a pre-morbid personality trait or if it was possible to change the impaired QoL. The results of the study showed that at Day 180 there was a decrease of 59% in mean lower UTI episodes compared to the previous 6 months (from 2.7 to 1.1; p<0.0001). The HAD score showed a highly significant (p<0.0001) decrease of 36% in the anxiety score, 25% in the depression score, and 32% in the overall HAD score. The improvement observed in depression, anxiety, and global HAD scores was significantly correlated to the reduction in mean number of UTI (p<0.0001). (Figure 7)

On Day 0, the HAD score showed that 80% of patients presented with anxiety, compared with 40% on Day 180, showing a significant reduction in the number of patients presenting with symptoms of anxiety. The Leicester score showed a significant improvement in daily activity score of 33% and feelings score of 55%, and the overall improvement was 44% (p<0.0001). The reduction in cystitis occurrences was significantly correlated to improvements in feeling (p<0.0001) and overall Leicester Impact scores (p=0.02). This observational study has shown that rUTI does have a major impact on QoL and indicated that successful management of UTI results in re-gained QoL.

Responders Profile and Evidence in Clinical Practice

Peter Tenke

Within 3 to 4 months of an initial UTI, 20–30% of women will have a recurrence. In addition, it has been shown that bacteriuria and urinary symptoms increase with age: 10% of women aged 40 to 65 years were treated for recurrent cystitis (rUTI).[7] rUTI should be categorised on the basis of age;

pre-menopausal women (15–50 years), healthy post-menopausal women (50–70 years, who are not institutionalised or catheterised), and elderly institutionalised women (who are catheterised in many cases). The risk of bacterial exposure and the risk of infection increase with age. In patients with concomitant disease, bacteriuria is associated with an increased mortality but the cause is usually the concomitant disease not the bacteriuria.[42]

The predisposing factors of UTI relating to age in pre-menopausal women are sexual intercourse, history of childhood UTI maternal history of UTI, diaphragm/spermicide use, previous antimicrobial treatment, and prior UTI. In post-menopausal women the predisposing factors are: UTI in childhood, UTI before the menopause, being a 'non-secretor', increased residual urine volume and increased rate of incontinence.[42]

OM-89 can be recommended for immunoprophylaxis in otherwise healthy women with recurrent uncomplicated UTI with LE: 1a, G: B in the EAU guidelines 2013.[42] However, its efficacy in other groups of patients is not fully established. A meta-analysis[43] demonstrated that with increasing age the risk of UTI was higher and that patients with increased risk factors gained greater benefit from OM-89.

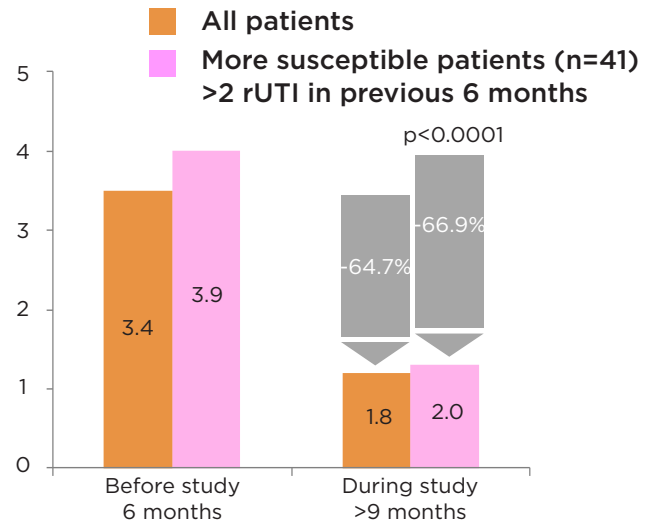
Market research[45] found that among women experiencing over 6 rUTI in a year, 33% were post-menopausal. They were less tolerant of the experience of rUTI and antibiotic side effects and sought alternative treatments (51% of the women who mentioned prevention were post-menopausal). The research concluded that post-menopausal women were at higher risk of UTI, were less tolerant of recurrences and were more reluctant to take antibiotics, and sought alternative preventative treatment.

Post-menopausal women experience oestrogen deficiency that can lead to alterations of the urogenital tract mucosa and this can promote frequent UTI. These women have usually had longer exposure to antibiotics, which contributes to their increased vulnerability to infections; by eradicating the periurethral flora, antibiotics may inadvertently enable colonisation and hence infection by new uropathogens. It is logical that OM-89 would be of great value to this group of patients, particularly as multiple exposure to antibiotics can also lead to increased resistance rates and the failure of antibiotics to cure.

The efficacy of OM-89 in post-menopausal women was evaluated in a small pilot open label, active control study in Poland.[46] The study included 55 post-menopausal women with recurrent uncomplicated UTI. Each patient was monitored for approximately 9 months, during which they received active treatment with OM-89 for 3 months, followed by 3 months of no treatment. In the final 3 months, the patients received 10 days of active treatment in each month. Efficacy was evaluated by comparing the number of episodes of UTI before and after treatment. The incidence of recurrences fell from 3.4 to 1.8 (time adjusted). Additionally, in a group of 41 women considered 'high risk' i.e., more susceptible to infections, the mean rate of recurrences fell from 3.9 to 2.0 ($p<0.0001$). The results of the study clearly showed a reduction in the number of UTI recurrences: 64% reduction overall, and almost 70% reduction in the higher risk group of patients. (Figure 8)

Oral immunotherapy with OM-89 has shown to be an effective prevention overall against rUTI in women between 18 and 72 years of age. In addition, in a sub-group of post-menopausal women with rUTI, OM-89 has shown efficacy and good tolerability.

Figure 8. Reduced incidence of rUTI in post-menopausal women treated with OM-89



CASE ILLUSTRATION

This case involved a 56-year-old woman with a medical history of UTI in adolescence, mild incontinence and an otherwise healthy urinary tract. In the pre-menopausal period between the ages of 25 and 50 she usually experienced 1–2 episodes of cystitis a year. In the post-menopausal period, the patient experienced an acute episode of cystitis and treated herself with fosfomycin trometamol 3 times. Despite this treatment the patient developed a new episode of cystitis and the GP prescribed 2 antibiotics for a period of 3 weeks (TMP/SMX for 2 weeks and ciprofloxacin for 1 week). Following the antibiotic treatment, the patient's symptoms recurred and she was referred to an urologist. Urine culture showed a multi-sensitive *E. coli*. The urologist commenced treatment with ofloxacin for 1 week followed by vaginal oestrogen therapy. The patient had a recurrence 3 weeks later; this pattern continued and she experienced a total of 25 episodes of cystitis in 2 years. Over a period of 2 years the patient received fosfomycin trometamol, ciprofloxacin, TMP/SMX, cefuroxime and amoxicillin plus beta-lactamase inhibitor. After the antibiotic treatment had ceased and a negative urine culture had been obtained, treatment with OM-89 was commenced. The patient had only 1 episode of cystitis during 3 months of OM-89 treatment and to date over a period of approximately six months has only experienced 1 further episode.

Patients with spinal cord injury are in a high risk group for rUTI. The neurogenic functional disorder of micturition that is responsible for chronic bladder retention enhances the risk of infection and stone formation. In patients with upper motor neuron lesions, detrusor-sphincter dyssynergia and excessive sphincter tone satisfactory voiding may be prevented and this causes vesicoureteral reflux with subsequent chronic pyelonephritis.[47] Antibiotics, such as aminoglycosides and cephalosporins, are useful in treating acute infection but protracted use should be avoided because prolonged administration could be nephrotoxic. Therefore, in this population, who are at an increased risk of rUTI, prolonged antibiotic use is not recommended and the use of alternative preventative strategies such as OM-89 should be considered.[48] The use of OM-89 as prophylactic treatment in spinal cord injury patients was assessed in a randomised, double blind, placebo-controlled crossover study.[49] The study population included 70 patients with spinal cord injury who had chronic lower UTI. The patients were divided into 2 sub-groups. The first group received OM-89 for 3 months, followed by placebo for 3 months. The second group received placebo for 3 months, followed by OM-89 for 3 months. The urine sample was taken from catheterised urine and therefore UTI was defined as bacteriuria ≥ 10^4 organisms/ml. The results showed that there was a significant decrease in UTI in OM-89 treated study group; particularly after 2 or 3 months when the effect of initial antibiotic treatment had stopped. There was no significant difference between the 2 treatment arms at the end of the study. (Figure 9)

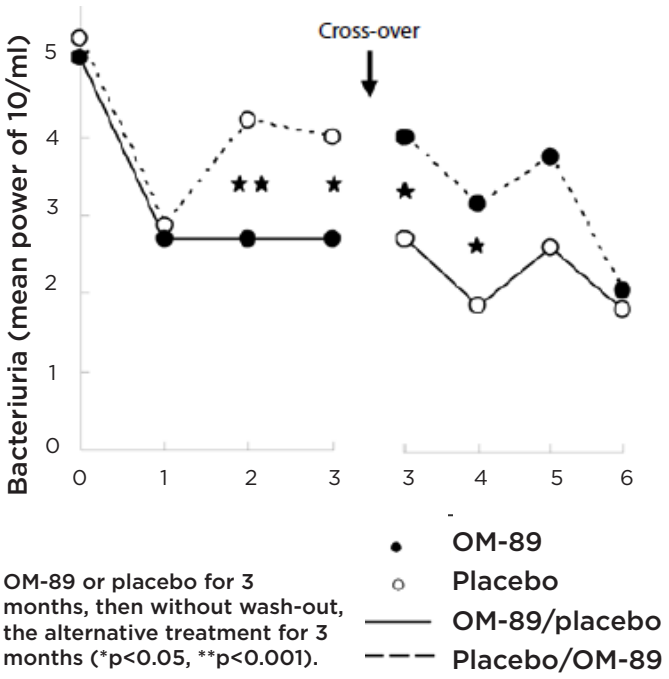


Figure 9. Evolution of bacteriuria over 6 months in two spinal cord injured patient groups.

The observed stabilisation of UTI in placebo patients in the second group may be explained by the carry-over effect of OM-89. Protection for several months after the withdrawal of therapy has been shown in previous observations.[43,46] The overall clinical efficacy and good tolerance of OM-89 provides new therapeutic possibilities in spinal cord injury patients with severe chronic UTI. Furthermore, a significant decrease in antibiotic prescription is an important asset for patients with neurogenic bladder dysfunction.

CASE ILLUSTRATION

This case involves a 42-year-old man who suffered a spinal cord injury in a traffic accident 5 years ago. The patient was using intermittent catheterisation for urinary retention, he had continuous bacteriuria and recurrent symptomatic episodes of UTI every 1–3 months. The patient was treated with several courses of antibiotics

(oflaxacin, ciprofloxacin, ampicillin + Beta Lactamase Inhibitor (BLI), TMP/SMX, and gentamycin). Subsequently, due to further recurrences he was prescribed TMP/SMX for 6 months as prophylaxis. During the 6 months of prophylactic treatment the patient had 4 episodes of UTI. He was admitted to the urological department due to a major symptomatic UTI; urine culture showed multi-resistant *E. coli* and the patient was given gentamycin for 5 days. Following this antibiotic treatment the patient was given OM-89 and despite the continued presence of bacteriuria has only had 2 minor episodes to date over a period of approximately six months.

A further high risk group of patients for rUTI are pregnant women. The effect of OM-89 was examined in 62 pregnant women[50] with bacteriuria. A statistically significant reduction of the incidence of UTI was seen; 19.4% incidence during pregnancy (and treatment with OM-89) compared with an incidence of 52.5% in the 6 months before pregnancy (p=0.0002). There was also a statistically significant reduction in the use of antibiotics (12.9% during pregnancy whilst receiving OM-89 compared with 55.7% in the 6 months before pregnancy, p=0.0002). All newborns were healthy and had normal Apgar scores. The results show that OM-89 is effective for preventing rUTI in pregnancy, and appears well tolerated in both mother and foetus. These examples illustrate that, in addition to being an effective prevention against rUTI in the general population of women between 18 and 72 years of age, OM-89 is effective and well tolerated in other groups of patients that are at high risk for rUTI.

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Increasing Evidence of Effectiveness of GAG Therapy in Different Forms of Cystitis

Summary of Presentations given at the IBSA Satellite Symposium 28th Annual EAU Congress, 15-19 March 2013

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The Scenario of Bladder Dysfunctions: Insights into the Therapeutic Potential of Glycosaminoglycan (GAG) Therapy

Pier Francesco Bassi

Diseases associated with bladder dysfunction impact significantly on a patient's quality of life, and since the origins of these conditions are unclear, they are difficult to treat and control effectively.

The epithelial lining of the bladder, the urothelium, serves to protect the bladder from any external damage (bacteria, chemotherapeutical or immunotherapeutical agents, radiation, etc). Understanding the role of the urothelium defect in mechanism of the associated diseases will afford a more in-depth understanding of the pathogenesis of the disease, and will ultimately provide patients with more adequate therapy.

The urothelium has an important glycosaminoglycan (GAG) layer; these GAGs are a class of polysaccharides, of which hyaluronic acid (HA) and chondroitin sulphate (CS) are key elements. Damage to the urothelium has been hypothesised to play a fundamental role in the pathogenesis of diseases associated with bladder dysfunction (Figure 1). As a result, the way in which we view these diseases and the therapeutic approach to their management is changing. Pathophysiologically, the focus is shifting to the restoration and maintenance of urothelium function rather than concentrating on the cause of the bladder damage.

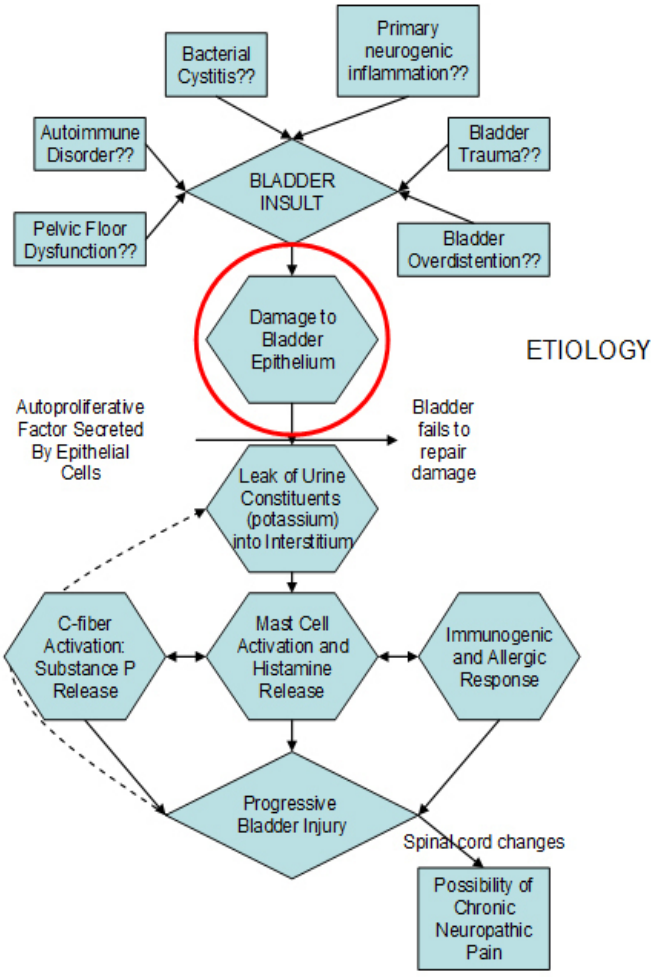


Figure 1. Pathogenesis of bladder diseases

A neuroinflammatory cascade has been proposed as a common factor of the so called 'GAG diseases'. In particular, the damage to the urothelium can result in the leakage of potassium (K+) into the interstitium of the bladder wall. The passage of K+ then causes activation of C-fibers, which promotes smooth muscle contraction, neurogenic inflammation, hypersensitivity, and pain.[1] The activation of C-fibers also results in the release of substance P. The release of substance P then promotes a neuroinflammatory cascade with the activation of mast cells and subsequent release of histamines. This exacerbates the disease's symptoms and transforms it from an acute condition into a chronic and progressive one. Such diseases include interstitial cystitis, painful bladder, chemical cystitis, bacterial cystitis, and overactive bladder.

The aetiology of chronic cystitis is still obscure, and although there is still limited evidence, damage to the urothelium is thought to be central to most bladder pathologies; the damage may originate from infection, primary neurogenic inflammation, oncology drugs or radiation, bladder trauma or overdistention, pelvic floor dysfunction, or an autoimmune response.[2]

As a result, new drug combination therapies, such as IALURIL® (HA and CS), are targeted towards the reduction of pro-inflammatory cytokines to allow for the repair of the urothelial protective layer, reduce permeability and restore its function as a barrier.

Management of Interstitial Cystitis/Bladder Pain Syndrome with Glycosaminoglycans (GAGs)

Mauro Cervigni

It is difficult to define interstitial cystitis/bladder pain syndrome (IC/BPS) because there are few specific diagnostic criteria established, no agreed pathophysiology, evaluation, or treatment.[3] IC has previously been defined as 'urinary urgency, frequency, and/or pelvic pain in the absence of bacterial infection'.[4] In 2003, ESSIC later renamed IC, giving it the broader title 'Bladder Pain Syndrome', and defined it as 'pain related to the urinary bladder, accompanied by at least one other urinary symptom such as day-time and night-time frequency, exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistention and biopsy if indicated'.[5] The bladder is the source of chronic pelvic pain in over 30% of female patients.[6]

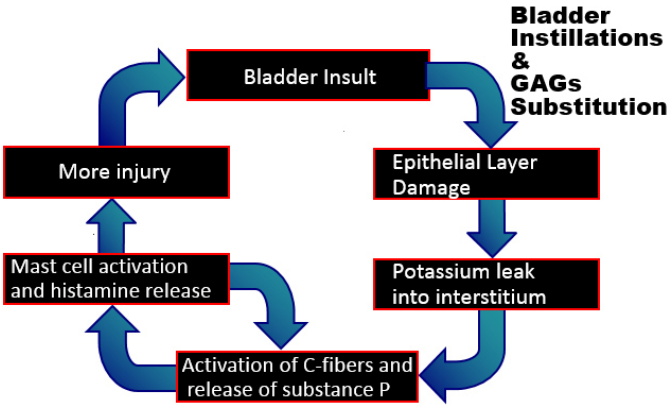


Figure 2. Principles of BPS/IC Therapy

There is a range of prevalence rates globally, and IC/BPS is viewed as a disease spectrum with different severities of symptoms. It is often diagnosed late in the disease continuum, with the average time between the development of symptoms and diagnosis being 5 years, and patients see at least 5 different physicians before they are diagnosed.[7-8]

IC/BPS may arise as a result of infection, autoimmune disorders, dysfunctional bladder epithelium, mastocytosis, neurogenic inflammation, toxic substances in urine, psychosomatic causes, or food intolerances. Regardless of the initial cause, the pathogenesis of the disease can be attributed to the dysfunction of the GAG layer, bladder mastocytosis, and neurogenic inflammation. Damage to or defects in the GAG layer lead to a cascade of events that begins with K+ leakage into the interstitium of the bladder, through to the release of substance P, which promotes the activation of mast cells and subsequent release of histamines; positive feedback in the cycle then results in sensory hyperstimulation. Principles of therapy for IC/BPS therefore are to restore epithelial function and the GAG layer, inhibit neural hyperactivity, control allergies, and modulate symptoms.

Treatment for IC/BPS takes the form of intravesicular therapy, the direct introduction of substances into the bladder via a catheter (also known as bladder instillation), and GAG substitution (Figure 2). There are various drugs which can be used in intravesicular therapy such as dimethyl sulfoxide (DMSO), which was the first drug approved by the FDA for the treatment of IC/BPS, and has been shown to have 53 to 80% success rate.[9] Other drugs that are used in IC/BPS treatment include sodium oxychlorosene, silver nitrate, hyaluronic acid, heparin, chondroitin sulfate, and anaesthetic solutions.

Various clinical trials have been conducted to investigate GAG substitution as a therapy, each demonstrating varying degrees of success. There are six main classes of GAGs: chondroitin sulfate, dermatan sulfate, keratan sulfate, heparin sulfate, heparin, and hyaluronan. Key components of the GAG layer include hyaluronic acid (HA) and chondroitin sulfate (CS), and so many of the trials have focussed on the instillation of these GAGs.

Intravesical hyaluronan infusion has been shown to reduce pain and, to a lesser extent, urinary frequency associated with IC.[10] Patients with positive potassium test results demonstrated beneficial effects with intravesicular CS treatments.[11]

Combination intravesicular therapy with HA and CS has been used to treat IC/BPS in patients where other conventional therapies have failed.[12] This combination therapy led to statistically significant decreases in symptom and problem scores in these refractory patients, with favourable tolerability and a positive adverse event profile. It is interesting to note that the study used 800 mg HA and 1g CS per instillation, which is 20 times the classical instillation of HA. Although the principal limit of this study is the lack of a control group with placebo, this preliminary experience is promising for the treatment of refractory IC/BPS, which in recent years has not benefited from effective new therapies. Furthermore, long-term follow-up, in which a small sample of patients were investigated for a further 3 years, confirmed the initial positive results.[13] Mean daily void (defined as the number of times the bladder is emptied in a day) at baseline was 17.8, and at 3 years was 11.9; the mean volume per void was 136.8 ml at baseline, increasing to 180.9 ml at 3 years, an increase of more than 40%, which demonstrated an improvement in bladder functioning. Intravesicular instillations of HA 1.6% and CS 2.0% over a period of 9 months produced a sustained improvement in symptoms, which was still apparent at 3-years' follow-up, in patients affected by IC/BPS unresponsive to previous treatments.

DMSO is the current 'gold standard' treatment for IC/BPS. A Phase III study for evaluation of efficacy and tolerability of IALURIL® (potassium ialuronate and chondroitin sulfate) versus Rimso® (DMSO) in 108 women (aged >18 years) affected by IC/BPS (primary diagnosis and resistant to first line therapies) will enable a direct comparison of the individual therapies. Other secondary endpoints that are to be assessed during this study include quality of life (QoL), economic impact in terms of cost, and the impact of frequency/filling pain. This study is ongoing.

Alternative therapeutic targets include modulating neuronal activity by the use of tricyclic and nociceptive blocker therapy, and the stabilisation of mast cell activity, which can be achieved through antihistaminergic therapy. Although these alternative targets may provide a good therapeutic approach, GAG substitution with bladder instillations is the main goal for the effective management of IC/BPS.

Efficacy of Glycosaminoglycans (GAGs) Treatment in Chemical and Radiation Cystitis

Enrico Finazzi Agrò

Literature regarding the efficacy of glycosaminoglycan (GAG) treatment for chemical and radiation cystitis is sparse, and thus evaluating the efficacy of GAG treatment is a challenging topic.

RADIATION CYSTITIS

There are several studies investigating the efficacy of GAGs in the treatment of radiation cystitis. A retrospective study investigated intravesical instillations of hyaluronic acid (HA) to reduce the acute vesical toxicity caused by high-dose brachytherapy.[14] Ninety-five clinical histories (with or without HA instillations) were reviewed over the whole 5-year study period, and the study found that the percentage of patients presenting with vesical toxicity was significantly lower in patients who had received HA (2.08% versus 12.8%; $p<0.05$). A Chinese study showed no difference when comparing intravesical HA instillation and hyperbaric oxygen in the treatment of radiation-induced haemorrhagic cystitis.[15]

A recent study suggested that prophylactic vesical instillations with 0.2% chondroitin sulfate (CS) may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynaecological malignancies. During radiotherapy, 40 ml of 0.2% CS was given weekly for 6 weeks, and the study found that the instillations were well tolerated by patients, and a decrease in overactive bladder symptoms, urgency, and frequency were observed.[16]

CHEMICAL CYSTITIS

A study investigating the efficacy of sodium hyaluronate (SHA) in the management of chemical and radiation cystitis was conducted in patients receiving radiotherapy (15 patients), BCG (Bacillus Calmette-Guérin, 24 patients),

and mitomycin C (30 patients). Weekly intravesical instillations of SHA were given for 8-24 weeks,[17] and after 4 weeks, bladder capacity had increased in all patients, and urgency and pain had disappeared. Overall, 67 patients (97%) reported the complete relief of dysuria and pain, and no adverse reactions were observed.

BCG is the standard treatment for patients with bladder cancer, and although BCG therapy is generally considered safe, it has potential local and systemic side effects, which may limit treatment use and result in treatment cessation. Treatment cessation has been observed in up to 30% of patients, with a delay or reduction in the number of instillations in 55-83% of patients.[18] In addition to problems with treatment adherence, it has been shown that for BCG to be effective, maintenance therapy is necessary; however, a study has shown that only 16% of maintenance patients received all their scheduled maintenance doses during a 3 year study period because of the adverse events (AEs) they experienced.[19] Therefore, reducing AEs is of paramount importance in increasing the efficacy of BCG in treating bladder cancer and improving the overall adherence to therapy.

To reduce local toxicity, the use of combination drugs has been suggested. Ofloxacin has been shown to lower BCG related moderate and severe AEs and improve patient retention in a study involving 115 patients.[20] Prulifloxacin has also been shown to decrease the incidence of local symptoms and improve the compliance to BCG intravesical therapy in 43 patients.[21]

Can GAG therapy help to reduce local toxicity in patients treated with BCG? A preliminary report in a small patient cohort (n=24) investigated the coadministration of HA and CS to reduce local toxicity. The primary variable was the Visual Analogue Scale (VAS) for bladder pain, and the secondary variables observed were International Prostate Symptom Score (IPSS), and bladder diary data. The drug combination was shown to avoid any increase in bladder pain and IPSS after BCG administration, and this result was statistically significant even in the small number of patients studied (Table 1).

Although this is a pilot study with no results on maintenance therapy these data support a possible role of HA and CS coadministration in reducing BCG local toxicity.[22] Whilst a correlation between BCG toxicity and efficacy has been hypothesised, a previous study did not confirm that BCG toxicity is actually related to improved outcome.[23] Thus, a reduced toxicity could likely result in improved patient adherence to therapy and possibly and improved outcome. These promising results in a small subgroup of patients should be confirmed and extended (and to exclude possible interferences of HA and CS on BCG efficacy) with further research.

Management of Recurrent Urinary Tract Infections with IALURIL®

Rocco Damiano

'Recurrent urinary tract infection' is defined as the presence of urinary tract infection (UTI) symptoms (urgency/frequency or dysuria) and 3 positive documented urine cultures in the previous 12 months.

Acute uncomplicated UTIs are extremely common clinical entities, being reported with an incidence of 0.7 episodes/year, and a recurrence rate of 25%. They are caused by E. coli in 75-90%[24] of cases and antibiotics are the mainstay of therapy.

The use of antimicrobials, mainly to treat the immediate symptoms, carries some limitations because of the risk of antibiotic resistance, the reduction in the efficacy of contraceptives, and the associated gastrointestinal effects with an increased risk of Clostidium difficile diarrhoea. A Cochrane Review has shown that after discontinuing prophylactic antibiotic treatment, there is a 0.82 relative risk per patient-year (relative to placebo) that patients would revert to their previous UTI frequency.[25] However, the risks associated with the long-term use of antimicrobials are the lack of long-term safety data, the small chance of severe side effects, and the

Table 1: Intravesical administration of hyaluronic acid plus condroitin sulphate to reduce local BCG toxicity: A randomised prospective pilot study.

All items: Mean ± SD

	BCG	BCG + HA/CS	p	BCG	BCG + HA/CS	p	BCG	BCG + HA/CS	p
	Pre-treatment			Post-treatment			Differences (post-pre)		
VAS	3,7 (3,3)	3,8 (2)	.94	4,8 (2,8)	2,8 (1,4)	.045	1,1 (1,8)	-0,9 (1,3)	.004
IPSS	8,8 (4,3)	9,4 (4,0)	.73	17,5 (8,8)	7,8 (2,6)	.001	8,7 (9,7)	-1,4 (1,9)	.0001
N° of daily micturitions	9,3 (2,8)	9,2 (2,2)	.91	9,5 (3)	9,3 (2,8)	.32	0,2 (1.9)	-0,9 (2,8)	.24

occurrence of breakthrough infections that are resistant to current antibiotics.

Moreover, one of the major issues is that inappropriate treatment of recurrent UTIs compromises the patient's quality of life (QoL). Recurrent UTIs can lead to sexual dysfunction in the form of sexual pain, and women with a history of recurrent UTIs more frequently develop irritative symptoms later, at time when they do not have an infection.

This, coupled with the unfavourable use of antimicrobials, means that an alternative approach to the treatment and management of recurrent UTIs is essential.

Bacteria adhere to the bladder sidewalls through filamentous proteins, which leads to activation of receptors on the surface of the epithelial cells. This process initiates a sequence of events; activated signalling pathways trigger internal cellular transcription of chemokines, and their subsequent secretion from the host cell leads to the recruitment of inflammatory cells, resulting in tissue inflammation. It has therefore been postulated that adhesion blockers (e.g., D-mannose) could be a potential therapy for treating UTIs.[26] In this context, glycosaminoglycan (GAG) therapy may also be a potentially beneficial approach, by inhibiting bacterial adhesion.

An experimental study in a murine model has shown potential benefits of GAG therapy with the reduction of the bacterial load in urine and thickness of the transitional epithelium.[27] From clinical studies, the use of such therapy has shown a significant reduction in the UTI rate for patients over a period of 12 months.[28-29]

From a recent randomised controlled trial, the prevention of recurrent UTIs by intravesicular administration of HA and CS – once a week for 4 weeks, with sterile urine, then once a month for the following 5 months – has led to a significant reduction (77%) in the UTI rate per patient/year over a 12-month period.[30] In addition, there was a prolonged median time to UTI recurrence; a decrease in pelvic pain and urinary/frequency (PUF) symptoms and total score; and QoL SF-36 also increased.

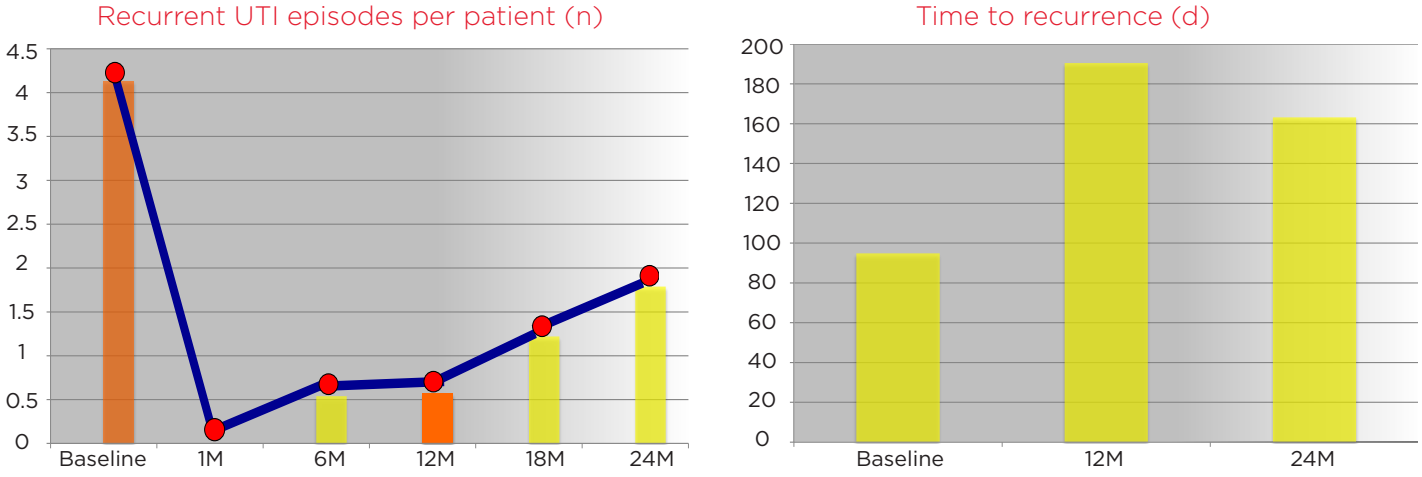
However, this study was conducted in one centre with a small number of patients. To overcome these limits, a retrospective analysis of the use of the IALURIL® on recurrent UTIs was required.

Recently, data from a multicentric (7 centres) retrospective study have validated these results.[31] This study featured the largest number of patients ever enrolled in a study using HA and CS combination for preventing UTI, and was conducted over a 24-month period. It confirmed the positive findings of the smaller study, with a prolonged time to UTI recurrence (Figure 3), a decrease in PUF score, and an increase in QoL as assessed by the SF-36. This multicentric study provided the largest amount of data related to 'real-life' clinical practice and the role of IALURIL® on recurrent UTIs.

Descriptive statistics and a binary logistic regression analysis have shown that the best candidates to benefit from this treatment are pre-menopausal females with a low rate of recurrent UTIs (from 3 to 4 per year), a BMI of 24 or below, and with normal bowel habits.

Bladder instillation of GAGs (e.g. IALURIL®: 1.6% HA and 2% CS) represents a new tool in the management of UTIs,

Figure 3. Multicentric retrospective study on HA and CS combination for preventing UTI



as targeting bacterial adhesion to bladder mucosa is a valid and essential alternative to the current widespread use of antibiotics.

Clinical Experience with IALURIL®: Results of a Multicentric Survey

Roman Tomaškin

It can be the case that promising new therapies demonstrating positive results in a clinical trial setting may not be practical, feasible, or replicable in the clinical setting. A multicentric survey[32] was conducted to obtain 'real life' data about the clinical efficacy and tolerability of a new treatment modality in a specific cohort of patients. These patients experienced bladder pain and other debilitating symptoms associated with bladder dysfunction, with a reduced quality of life (QoL), and previous treatment with standard therapies proving ineffective.

The study was conducted in 60 patients in outpatient clinics (95% female subjects) who received intravesical instillations of hyaluronic acid (HA) and chondroitin sulfate (CS). Most cases (over 50%) were patients with recurrent cystitis with a clinical failure of the standard therapeutic approach (antibiotics in full dose followed by prophylactic regimen, immunostimulation, behavioural techniques etc[33-34]). Thirty two patients had recurrent cystitis, 19 patients had interstitial cystitis/bladder pain syndrome (IC/BPS), 7 patients had post-radiation cystitis, and 2 patients had post-chemotherapeutic cystitis.

To evaluate the treatment efficacy and tolerability of IALURIL®, a questionnaire for the subjective evaluation of the therapeutic response and tolerability was completed by both the urologist and the patient; the VAS, objective measurements of bladder function, and the O'Leary-Sant questionnaire[35] were also used.

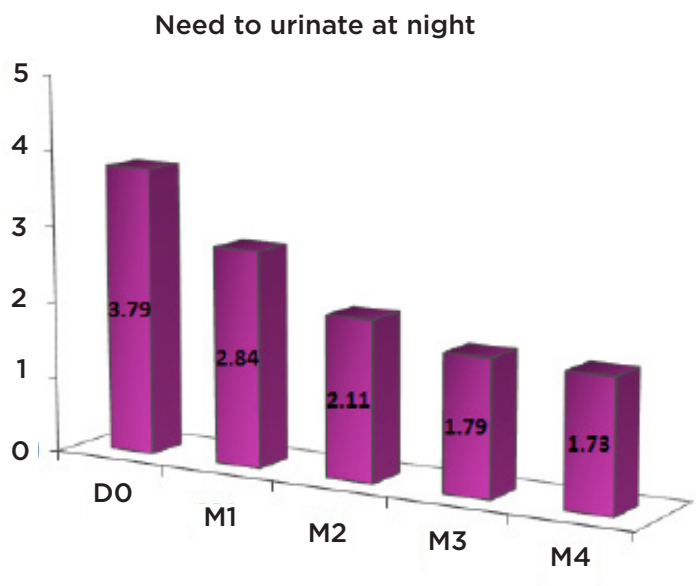
Both urologists and patients recorded improved efficacy and tolerability of treatment following the intravesical administration of IALURIL®. Treatment tolerability was rated as 94.6% and 97% satisfaction (answering excellent or good), by urologists and patients respectively.

The VAS was used to evaluate changes in the four main domains of symptoms. These were: perception of pain, voiding frequency, voiding urgency, and quality of life during treatment. A statistically significant improvement following IALURIL® treatment was observed in all four domains.

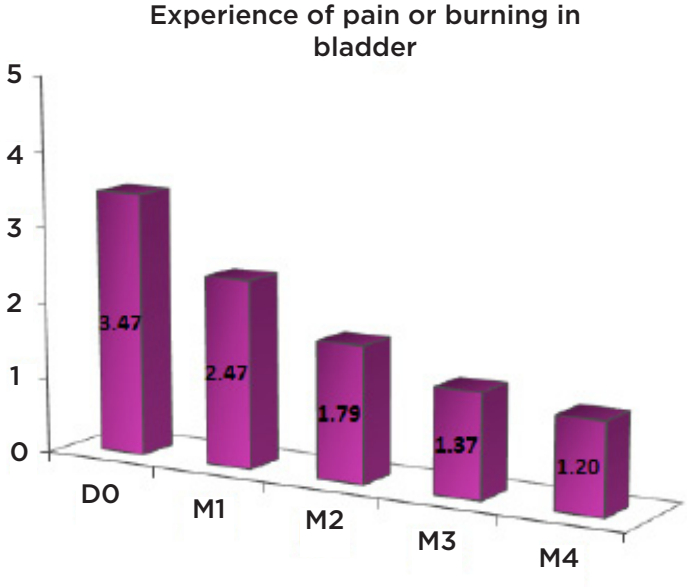
Intravesical treatment with IALURIL® also resulted in a statistically significant improvement in voiding parameters, such as mean number of voids (almost 50% reduction), and mean voiding volume (increase from 130ml to 200ml).

In the subgroup of patients with recurrent cystitis, 67% of patients used antibiotics at the time of entry into the study, but at the final visit less than 10% of patients were using antibiotics. Similarly, almost 40% of patients suffered

Figure 4. Clinical experience with IALURIL®: Results of a multicentric survey in Slovakia.
O'Leary – Sant questionnaire IC Symptoms Index



5 - 5 times per night, 4 - 4 times per night, 3 - 3 times per night, 2 - 2 times per night, 1 - Once per night, 0 - Not at all



4 - Almost always, 3 - Usually, 2 - Fairly often, 1 - A few times, 0 - Not at all

from clinically symptomatic inflammation at the entry visit, but less than 10% of patients experienced persistent symptoms after treatment.

In the subgroup of IC/BPS, post-radiation and post-chemotherapy patients, the O'Leary-Sant questionnaire clearly showed sustained improvement in all domains (voiding urgency, voiding frequency, nocturia, and pain). A statistically significant reduction in the total IC Symptom Index was observed; similar results were seen in the IC Problem Index, and the reduction observed was also statistically significant (Figure 4).

This multicentric study demonstrated significant efficacy and favourable tolerability of the intravesical administration of IALURIL® (HA and CS combination) in the treatment of recurrent UTIs, IC/BPS, and chemical and radiation cystitis. This study also demonstrated that data obtained from research and well conducted randomised studies were valid in real life clinical praxis.

Final Remarks

Pier Francesco Bassi

The different clinical entities that were in the past considered distinct diseases can now be viewed as diseases caused as a result of the dysfunction of a common physiological element, the urothelium and associated GAG lining. This renewed approach to looking at the pathophysiology of these GAG diseases will allow the development of more effective treatment regimens for the treatment of these debilitating and sometimes chronic diseases. New drug combinations, such as HA and CS (IALURIL®) have shown great promise in the clinical setting, and further research is necessary to expand and confirm these new ideas.

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Towards Individualisation of Prostate Cancer
Towards Individualisation of Prostate Cancer Treatments: From Bench to Bedside

Summary of Presentations given at the Ipsen Symposium 28th Annual EAU Congress, 15-19 March 2013

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Towards Individualisation of Prostate Cancer Treatments: From Bench to Bedside

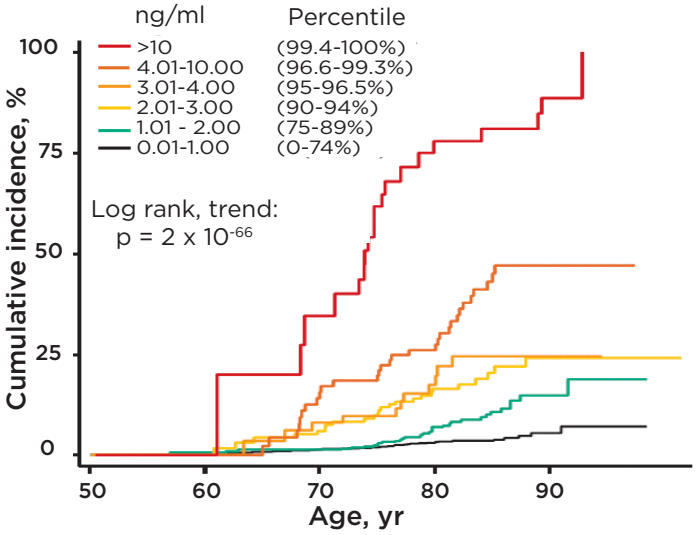
Peter Hammerer

Prostate cancer is the most commonly diagnosed cancer in men. Patient management requires a 3-step approach: step 1, identification of the patient's profile using biomarkers and staging tools; step 2, based on the findings in step 1, individualisation of the patient's treatment using nomograms, guideline recommendations, and balancing the treatment according to comorbidities, patient preference, and aspects of quality of life. Step 3, (the goal) to achieve improvement of patient support by communication, opportunities for new investigational therapies, and establishing a multidisciplinary team.

The 2013 cancer statistics show that prostate cancer is the second leading cause of death in men.[1] However, there is continued debate surrounding screening for prostate cancer using the Prostate Specific Antigen (PSA) test. The US Preventive Services Task Force conducted a comprehensive review of the medical evidence surrounding PSA screening, including the results of recently completed large clinical trials.[2] Following the review, they issued a recommendation statement on PSA screening; 'The US Preventive Services Task Force recommends against PSA-based screening for prostate cancer. Potential benefit does not outweigh the expected harms.' The American Urological Association disputed the US recommendations on prostate cancer screening stating 'it is inappropriate and irresponsible to issue a blanket statement against PSA testing, particularly for at-risk populations. Men who are in good health and have more than a 10-15 year life expectancy should have the choice to be tested and not discouraged from doing so.'

In fact, PSA has been shown to be a useful indicator of prostate cancer risk. PSA was measured in plasma samples obtained between 1981 and 1983 in a study involving

Figure 1. Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. Results from a study of 4,383 men from Copenhagen City Heart Study. Orsted D, et al. Eur Urology. 2012;61(5):865-874



4,383 men in Copenhagen. During a 28 year follow-up period the study found that men with an elevated PSA had a very high chance of developing prostate cancer 20 years later, and men with a very low baseline PSA had a very low risk of developing prostate cancer. [3]

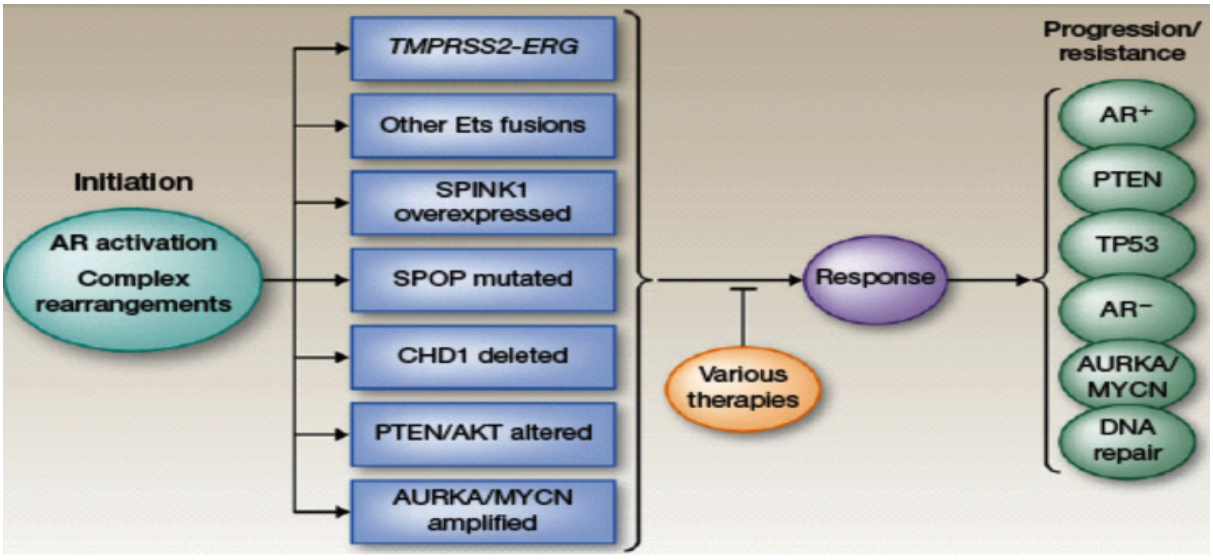
However, following PSA testing, it is difficult to assess when to perform a prostate biopsy. This decision can be assisted by using one or more of 3 methods. Firstly, testing for the number of circulating tumour cells and identifying biomarker qualification.[4,5] This approach is useful in selecting patients with advanced cancers and in selecting beneficial treatments. Secondly, testing urine for the presence of the PCA3 antigen. This test has been approved by the FDA for men who have previously had a negative biopsy. Thirdly, the T2:ERG test. This urine test looks for the fusion of 2 genes; one that codes for transmembrane serine 2 protease (TMPRSS2), which is an androgen-responsive transmembrane serine protease that is fused to an Ets oncogenic transcription factor called ERG (Ets-related gene). This TMPRSS2-ERG fusion is very important in the development of prostate cancer. The function of TMPRSS2 in prostate carcinogenesis relies on the over expression of Ets transcription factors such as ERG, and this influences many factors that are necessary for prostate cancer development such as proliferation, anti-apoptosis, genomic instability, differentiation, angiogenesis, cell migration and invasion.[6]

The value of using urine PCA3, TMPRSS2 and ERG gene fusion (T2:ERG) tests was shown in a recent study,[7] in addition to these tests the study used a new test, serum [-2] proprostate-specific antigen ([-2]proPSA) prostate health index (Phi). The study population consisted of 246 men before prostate biopsy, 110 (45%) of the men were diagnosed with prostate cancer and 136 (55%) men showed no evidence of malignancy. The PCA3, Phi and T2:ERG tests were performed in both groups of men and showed areas under the receiver operating characteristic (ROC) curve (AUCs) of 0.74, 0.68 and 0.63 respectively, indicating a significant difference between men with malignant prostate biopsy and men with benign prostate biopsy. However, the combination of both markers (PCA3 and Phi) enhanced diagnostic power but showed only a small improvement of AUC from 0.01 to 0.04.

New strategies in prostate cancer testing can help with decisions relating to treatment choices in the clinical environment. For example, the use of genomics may enable the identification of the ideal candidate for a particular type of treatment.[8] However, some patients will progress to cancer despite local or systemic treatment, and in this instance an alternative treatment is required that can be selected using further genomic analysis.

The well-established pathology of breast cancer has the potential to help with the development of prostate cancer treatment. In breast cancer, there are 2 suppressor genes BRCA1 and BRCA2, which are similar to genes involved in prostate cancer. Mutations of these genes are linked to the development of hereditary breast and ovarian cancer. It has been shown that women who have mutation of BRCA1 or BRCA2 have a risk of getting breast cancer of between 40% and 85%, which is 3 to 7 times greater than that of women who do not have the mutation. The identification of specific genes in breast cancer enables

Figure 2. New strategies in prostate cancer: translating genomics into the clinic.
Beltran H, Rubin MA. Clin Cancer Res. 2013



treatment to be targeted. For example, in HER2+ breast cancer sufferers, the HER2 gene is overexpressed. This mutation is treated with Herceptin (trastuzumab) – a drug that specifically targets the HER2 gene. This type of targeted genetic treatment would be invaluable in the treatment of prostate cancer.

Learnings From Breast Cancer Management in Treatment Individualisation (Biology and Treatment Strategy)

Giuseppe Curigliano

The genomic portrait of breast cancer shows that this is not one single disease but different breast cancers; the Luminal A, Normal-like, Luminal B, HER2-enriched and Basal-like breast cancers.

The genetic portrait of breast cancer can be mapped to show the down-regulation and up-regulation of specific genes. This means that within any kind of tumour, genes that 'drive' information can be identified, and the remaining genes considered 'passenger genes' and are not up-regulated. The clinical implication is that in breast cancer there is not only a prognostic signature, but a signature that is predictive of response to a specific targeted agent. Therefore, the aim is to treat patients according to genomics. Using tissue analysis, specific genetic mutations or specific genetic alterations can be identified and used to predict a patient's response to a treatment. This approach to breast cancer diagnosis and treatment provides personalised medicine.

The subtypes of breast cancer that have been identified allow further clarification of the different types of breast cancer. Each type has a different prognosis and requires different treatment. For example, Luminal A (HER2 Negative) breast cancer has a good prognosis: 90% of patients survive for 20 years after first diagnosis, and chemotherapy is not required. The genetic portrait of Luminal A cancer shows genetic stability and all the genes are down-regulated, resulting in a straightforward cure, e.g. by using Tamoxifen. Luminal B (HER2 positive) cancer occurs in 70% of patients and is endocrine responsive. This is more complex as there are other pathways that can reduce responsiveness to endocrine therapy necessitating a different approach to treatment. In this type of cancer there is not a single mutation or a single 'driver' gene, there is a network of 'drivers' and 'passengers' involved. This means that if a pathway is down-regulated, an upward regulation of another pathway can arise.

The genes most frequently mutated in breast cancer are the tumour protein 53 (TP53) (23%) and phosphatidylinositol-4,5 bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) genes (26%).[9] Likewise, PIK3CA is commonly found in bladder and prostate cancer.

Can this level of molecular characterisation be integrated into treatments for breast cancer?

There are common constituents that characterise tumour development. These include sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.[10]

In breast cancer, data from next generation sequencing can provide the circos plot of genomic analysis.[11] This analysis shows the characteristic of any single chromosome, specific mutation, amplification, or translocation between one chromosome and another. Subsequently, 'driver' pathways can be located for individual cancer types, and a specific therapy selected according to the individual circos plot. For example, for a patient who is human epidermal growth factor receptor 2 (HER2) positive a fluorescence in situ hybridization (FISH) test is required to positively identify HER2. A genetic analysis of the specific mutation is required in order to stratify or treat the patient.

The genetic portrait of breast cancer shows that different, specific treatment is needed for each of the subgroups of cancer. Before 1998, the only treatment option available was chemotherapy. There was no stratification according to risk, and the long-term side effects in terms of cardiotoxicity and loss of fertility had a dramatic impact on the life of the patient. Currently, there are more treatments available; for instance if HER2 cancer is treated for a year with trastuzumab a 50% rate of cure can be achieved.[12] Basal-like breast cancer has traditionally been difficult to treat but in the future, due to genetic profiling, it may be possible to treat using a poly ADP ribose polymerase (PARP) inhibitor. In Luminal breast cancers, different treatments are required; Luminal A cancer treatment is relatively straightforward using tamoxifen. However, the treatment of Luminal B is more complex because of the increase in proliferation of other pathways, and treatment requires the alternative pathways to be blocked. Therefore, treatment for Luminal B cancer necessitates tamoxifen in combination with a new, targeted agent aimed at reversing resistance.

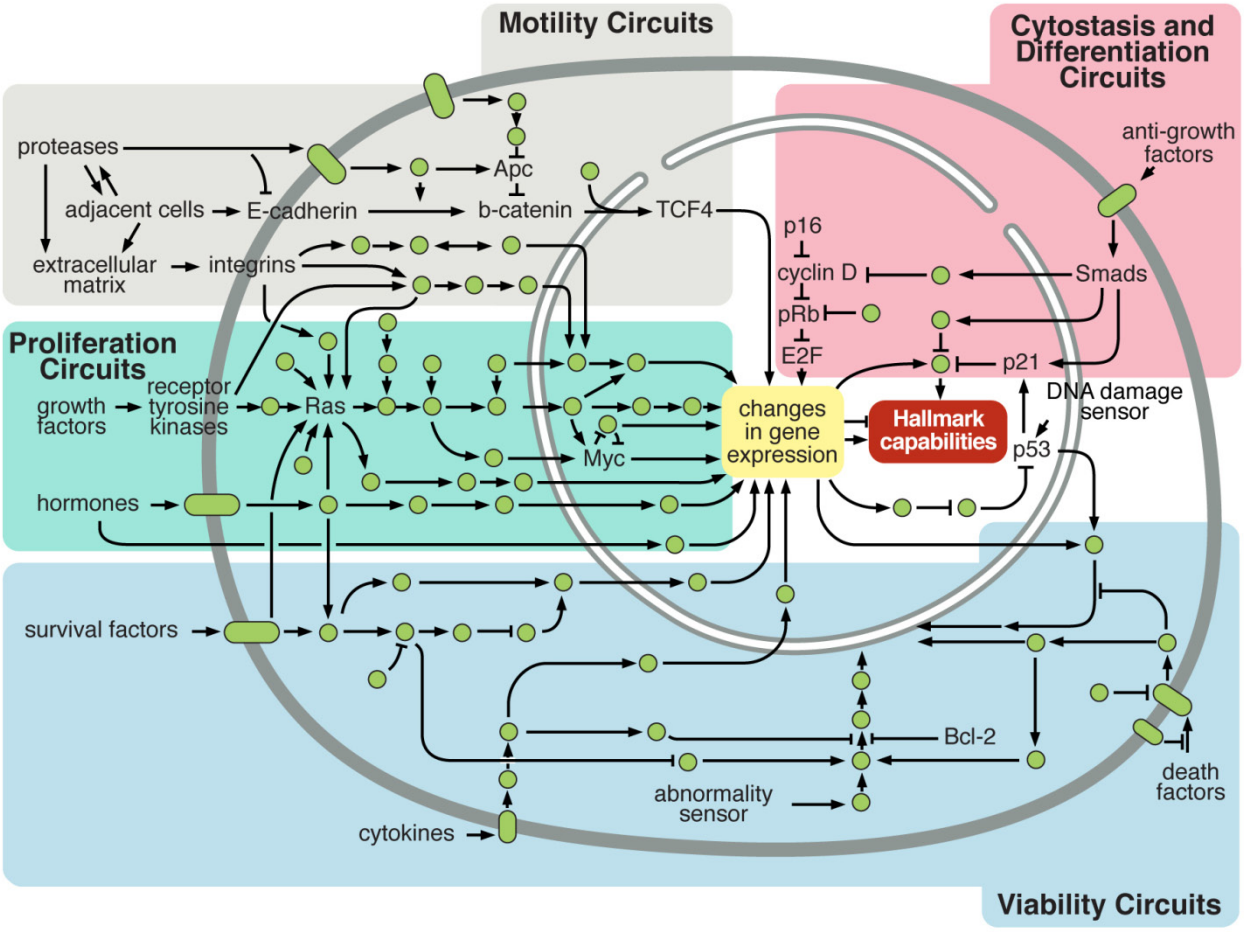


Figure 3. Intracellular signaling networks regulate the operations of the cancer cell.
Hanahan & Weinberg. Cell 2011;144:646-674

There are different agents that can be used to target HER2 breast cancer, such as trastuzumab and T-DM1. These agents function by causing the molecular antibody to bind to the receptor on the cell, causing internalisation of the complex, and release of the chemotherapeuticagent within the tumour cell. There is no systemic toxicity produced by this process, and there are few side effects because the treatment is localised. The drug T-DM-1 has been approved by the FDA for the first line treatment of patients with metastatic breast cancer that is HER2 positive.

Dual-targeted treatment involves combining 2 different mechanisms of action. For example, pertuzumab and trastuzumab have complementary mechanisms of action; trastuzumab inhibits-ligand-independent HER2 signalling, activates antibody-dependent cell mediated cytotoxicity (ADCC) and prevents HER2 extracellular domain (ECD) shedding. Whilst pertuzumab has a different mechanism of action - it inhibits ligand-dependent HER2 dimerization and signalling and activates ADCC.

The NeoSphere study[13] investigated dual targeting. 417 HER2 positive patients were randomised before surgery to 4 treatment arms:

1. docetaxel (a chemotherapeutic agent) + trastuzumab
2. docetaxel + trastuzumab + pertuzumab
3. trastuzumab + pertuzumab (this arm did not include chemotherapy)
4.docetaxel + pertuzumab

The overall results showed a dramatic increase (45%) in complete pathological response. The arm of patients with dual targeting without chemotherapy showed 29% complete pathological response (i.e. reduction of the tumour) for patients with oestrogen receptor (ER) negative cancer. However, in the HER2 positive population, there is a single 'driver' (HER2) and no estradiol receptor. This enables the driver to be targeted, and in breast cancer, the pathological complete response rate correlates with survival, therefore 90% of these patients have a probable life expectancy without disease of 5 years.

In Luminal B breast cancer a different treatment strategy is required: the combination of 2 different agents. This entails endocrine therapy combined with agents that can target 'drivers' of a system. In Luminal B cancer, the

target is the rapamycin (mTOR) pathway. In this pathway, mTORC1 activates the ER in a ligand-independent fashion.[14] Oestradiol suppresses apoptosis induced by the P13K/mTOR blockade[15] and in endocrine-resistant breast cancer cells, the P13/mTOR pathway is hyperactivated.[16] Therefore, the targeting of mTOR enhances the efficacy of hormonal therapy.

Basal-like or triple-negative breast cancer is characterised by the mutation of BRCA 1 and BRCA 2. Patients with this type of mutation have a risk of developing breast cancer of around 50% in their lifetime. This type of tumour is very aggressive and the patients are usually under 40 years-old. BRCA is involved in the mechanism of resistance as well as the mechanism of DNA repair. Therefore, the treatment of these patients requires a target agent that can interfere with DNA repair and another agent that will reduce other damage (the PARP inhibitor). Tutt et al.[17] studied the efficacy of PARP inhibitors in BRCA 1 and BRCA 2 mutated breast cancers and showed an increase in progression free survival. O'Shaughenessy et al.[18] investigated metastatic triple-negative breast cancer and PARP inhibition, and compared gemcitabine and carboplatin with or without iniparib (a small molecule with PARP-inhibitory activity). The study found that the clinical benefit and survival of patients improved in patients who received gemcitabine and carboplatin with iniparib; the median progression free survival was increased from 3.3 months (in patients who did not receive inparib) to 5.9 months (in patients who received iniparib) (p=0.01).[18]

There are 'hallmarks' of cancer that constitute an organising principle that can be used to rationalise the complexities of malignant disease. Recognising the hallmark traits of cancer cells, for example PARP inhibitors, and the widespread applicability of these hallmarks will help in the development of new treatments of cancer.[10]

There is no single disease for any type of cancer. Additionally, there are different oncogenic events that can be shared across molecular classes. For each of these molecular events there is an established first-in class agent. In cases of progressive disease with both down- and up-regulation, a second-in-class drug is required to reverse resistance and used according to molecular profiling. The 'integrated biology' approach could help improve results in patients who develop resistance, offering them the opportunity of increased life expectancy.

Will Future Biomarkers Kill PSA? Results of the Triptocare Study

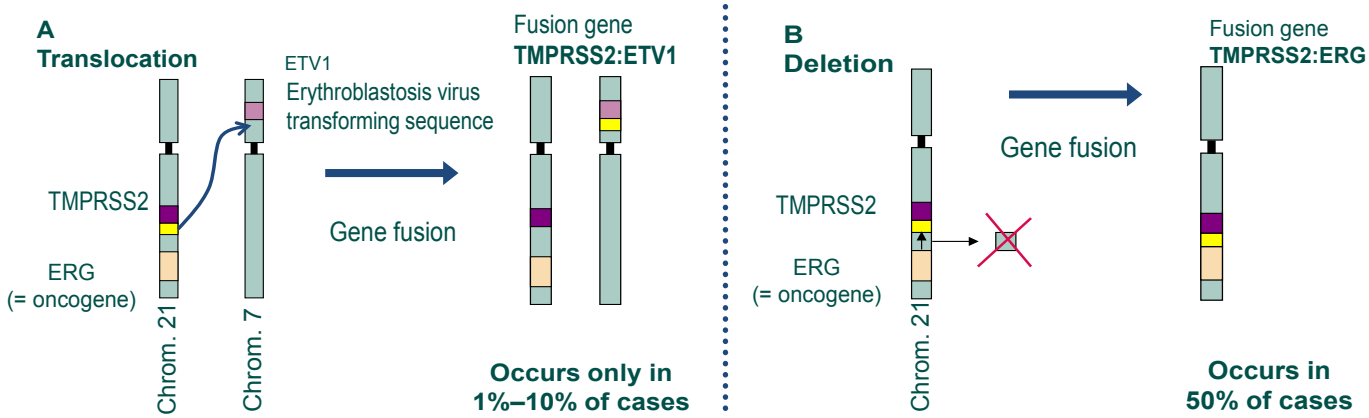
Luis Martinez Piñerio

The objective of the Triptocare[19] study was to understand the correlation between changes in prostate-specific antigen (PSA) levels, testosterone levels, biomarker kinetics, and eventually disease progression post-androgen-deprivation therapy. This was a multicentre, international study involving 322 patients with newly diagnosed advanced prostate cancer. At baseline, the patients were tested for PSA level, prostate cancer gene 3 (PCA3) status, transmembrane protease serine 2-transcriptional regulator (TMPRSS2-ERG) status and testosterone levels.

PCA3 can be isolated as non-coding messenger ribonucleic acid (mRNA) from first catch urine specimens after prostate massage and is highly overexpressed in prostate cancer cells. The PCA score has good sensitivity and specificity for predicting positive repeat prostate biopsies, and in localised prostate cancer may show correlation with tumour volume. This has been shown in the diagnosis of small volume prostate cancer but has never been used in patients with advanced prostate cancer.

TMPRSS2-ERG status is important because gene fusion can transform a normal cell into a cancer cell. There are 2 ways that gene fusions occur in prostate cancer; translocation or deletion.[20] Translocation occurs in only

Figure 4. Gene fusions in prostate cancer. Tomlins, et al. Science. 2005;310:644.



1%-10% of cases, the gene TMPRSS2 that is located in the long-arm of chromosome 21 translocates to the short-arm of chromosome 7 and fuses with the ETV1 gene to create a new, fusiongene, TMPRSS2-EVT1. In 50% of cases, a deletion in the long-arm of chromosome 21 occurs. The gene TMPRSS2 and the oncogene (ERG) fuse, creating the fusion gene TMPRSS2-ERG. This gene transforms the prostatic cell into a cancer cell.

Individualised care is the motto today for oncology patients, including those with prostate cancer. Since the 1990s, prostate specific antigen (PSA) has been used as a biomarker for prostate cancer, enabling better detection and earlier treatment of this often slow-progressing but sometimes aggressive disease. However, PSA is not the ideal marker for determining the seriousness of prostate cancer; therefore new biomarkers are currently being investigated. These include prostate cancer gene 3 (PCA3) and gene fusions of the type 2 transmembrane serine protease (TMPRSS2) with v-erythroblastosis virus E26 oncogene homolog (ERG; TMPRSS2-ERG gene fusion). These urine biomarkers are potentially more specific for determining the presence and aggressiveness of prostate cancer. It is known that PCA3 mRNA is over-expressed in malignant prostate tissue when compared with benign prostate tissue. Today assays are available to accurately measure PCA3 mRNA and PSA mRNA, and the PCA3 score derived from these measures has good sensitivity and specificity for predicting a positive repeat prostate biopsy. This test is already commercially available for determining the usefulness of performing additional biopsies. TMPRSS2-ERG is the most common gene fusion in prostate cancer, occurring in approximately 50% of all cases and can be associated with aggressive or recurrent disease. As such, the TMPRSS2-ERG score may be considered as a prognostic indicator in prostate cancer, although more research is still required.

Using a combination of TMPRSS2-ERG and PCA3 scores may significantly improve the sensitivity of prostate cancer diagnosis and prognosis and, based on these assumptions, Ipsen performed a multicentre European clinical trial in hormone-naïve patients with locally advanced or metastatic prostate cancer. This study is the first to analyse biomarkers in a more advanced disease stage. Both biomarkers were measured at baseline and during triptorelin treatment over a period of 6 months.

A paper summarising all the results has been submitted to a peer review journal and feedback is expected shortly.

PSA: Imperfect but Still the Best?

Alan Thompson

Prostate-specific antigen (PSA) is a 33 kilodalton (kDa) glycoprotein with 232 amino acids found on the long-arm of chromosome 19. It is a Kallikrein family serine protease (1 of 15) found in prostatic ducts at a concentration a million times more concentrated than in serum (0.4-5.0 mg/ml). PSA liquefies the seminal coagulum and is produced by the epithelial cells of the prostate. Any disruption of the cells, such as infection, trauma or inflammation, causes diffusion of PSA into surrounding tissues and the blood. It is thought that prostate cancer cells per se produce less PSA but are greatly increased in number.

The causes of increased PSA are prostate cancer, benign prostate disease, infection (prostatitis or urinary tract), any form of trauma (including cystoscopy, catheter or a biopsy), acute urinary retention, ejaculation in men over 50 years-old and significant exercise. The causes of decreased PSA are definitive cancer treatment, surgical or medical castration (prostate removal or hormone therapy), the use of 5 alpha reductase inhibitors in conditions such as benign prostatic hyperplasia or hair loss, ejaculation in men less than 40 years-old, and Saw Palmetto (which used to contain PC-Spes which decreased the level of PSA).

'Prostate specificity' is a myth. Over the years there have been reports that PSA was detected in Skene's gland (female paraurethral gland) and in 1987 it was reported to have been found in tumours. There have been case reports of PSA staining (immunohistochemistry) in bladder tumours, cystitis glandularis, breast tumours and adnexal tumours. In addition, it has been reported that ultrasensitive assays[21] could detect PSA in breast milk, breast cysts, nipple aspirates, amniotic fluid, female serum, cerebrospinal fluid and saliva. These reports are questionable as PSA measurement is prostate specific.

There is no 'normal' PSA level, because in clinical practice a 'normal' PSA is defined as being lower than an absolute figure. In the early 1990s Catalona et al.[22] attempted to discover the absolute figure of PSA, and defined PSA of 0-4 ng/ml as the cut off for biopsy. Therefore, biopsies were only performed when PSA measurements were greater than 4 ng/ml. The results showed that in a PSA measurement of between 4 and 10 ng/ml, 26% of the biopsies taken were positive and in patients with a PSA greater than 10 ng/ml, a positive result was seen in 53% of the biopsies that were taken. Subsequently, a PSA measurement of 4 ng/

ml was defined as the 'normal' measurement based on ROC analysis. Using this cut off has been shown to have a sensitivity of 67.5–80% and a specificity of 60–70%. The measurement of PSA as a positive predictive value (PPV) has shown that a PSA measurement of 20-29 ng/ml had a PPV of 74%, a PSA of 30-39 ng/ml had a PPV of 90% and a PSA of 50-99ng/ml had a PPV of 100%. Collectively, all measurements greater than 20 ng/ml had a PPV of 87%.[23] It should be noted that the threshold for biopsy is determined by verification bias i.e. patients with a PSA of less than 4 ng/ml are biopsied; the total number of cancers is not known. This was indicated in a study that used the threshold for biopsy of greater than 4.1 and found that 82% of cancers in younger men (less than 60 years-old) were not detected and 65% of cancers were not detected in older men.[24]

The prostate cancer prevention trial[25] found that in a significant number of patients with PSA measurements of less than 4 ng/ml, a positive biopsy was obtained. (Table 1)

PSA derivatives can be used to help to predict prostate cancer progression and disease management. These include age-specific PSA, PSA density, complex PSA density, PSA density of the transition zone, PSA velocity, PSA doubling time, free to total PSA and PSA isoforms.

AGE SPECIFIC PSA

There is an association between age and serum PSA. If age-specific PSA reference ranges are used the sensitivity of PSA is improved and therefore the detection of curable organ-confined disease in younger men. Partin et al.[26] reviewed 4,597 records and found that if a PSA of 4.0 ng/ml was used as a cut off value, there was an 82% cancer detection rate. However, if an age-specific range was used, the detection rate decreased to 78%, although 18% more cancers were detected in younger men (less than 60 years-old) and 22% less cancers were detected in older men (more than 60 years-old). Based on these findings, the American Cancer Society National Prostate Cancer Detection Project concluded that age-specific ranges increased specificity, and although they decreased sensitivity, they should be used.

Table 1: PSA at biopsy and number of positive biopsy results

PSA at biopsy (ng/ml)	Number of patients	Number of positive biopsies (%)
0.6 - 1.0	1277	112 (8.8)
1.1 – 2.0	998	170 (17.0)
2.1 – 3.0	482	115 (23.9)
3.1 – 4.0	193	52 (26.9)

PSA DENSITY

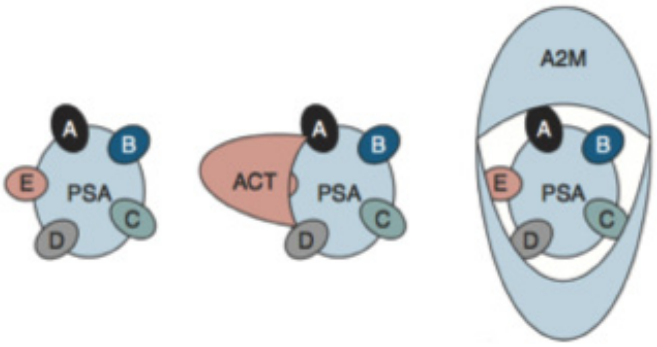
Volume based parameters include normal PSA density, complex PSA density and transition zone PSA density. Biopsy is recommended if the PSA level is 4-10 ng/ml and the density is greater than 0.15.[27] PSA density also predicts tumour upgrading following a biopsy after a radical prostatectomy, Corcoran et al.[28] found that in biopsies of moderate (3+3) and low risk tumours (3+4) the tumours were upgraded in patients with a higher PSA density (odds ratio 1.46 and 1.37 respectively). However, higher grade tumours produce less PSA per unit volume and so PSA density loses its predictive value.

PSA VELOCITY

The Baltimore longitudinal study of ageing[29] found a significant difference in age-adjusted rate of change in PSA level among men with prostate cancer, benign prostate hyperplasia and no prostate disease. The study suggested that prostate cancer development could be predicted from frozen sera in patients: a positive prediction was given if the PSA measurement increased by more than 0.75ng/ml per year. D'Amico et al. suggested that PSA velocity may have a role in predicting aggressive life-threatening prostate cancer. The study found that a PSA velocity greater than 0.35 ng/ml per year predicted prostate cancer 10 to 15 years prior to diagnosis. In addition, the study indicated that a PSA velocity greater than 2.0 ng/ml per year during the year prior to diagnosis is predicative of cancer-specific mortality following radical treatment.[30]

Measurable PSA is found circulating in the blood in complexed (bound cPSA) or unbound (free PSA) forms. The 3 proteins that bind PSA are: alpha 1-antichymotrypsin (PSA-ACT); Alpha 2-macroglobulin (PSA-A2M); Alpha 1 protease inhibitor (PSA-API) and free PSA. Free PSA has 5 epitopes and when PSA-ACT is added, 2 epitopes are left free, allowing easy measurement using an antibody. If PSA-A2M is used, the epitopes are all covered and PSA cannot be found.

Prostate cancer cells produce the same amount of PSA as benign cells, however PSA from malignant cells escape



Measurable PSA found circulating in the blood exists in complexed (bound, cPSA) or unbound (free PSA) forms.

3 proteins known to bind PSA	% in serum
Alpha 1-antichymotrypsin (PSA-ACT)	60–90
Alpha 2-macroglobulin (PSA-A2M)	10–20
Alpha 1 protease inhibitor (PSA-API)	1–5
Free PSA (PSA has 5 epitopes)	5–40

Figure 5.Molecular derivates of PSA

proteolytic processing. Men with prostate cancer have a greater fraction of serum PSA complexed to ACT and a lower percentage of total free PSA,[31] indicating that the percentage of free PSA provides additional specificity for prostate cancer detection. The difference is greatest when comparing men with benign prostate hyperplasia, prostate cancer and no prostate disease. Free PSA is more useful in PSA measurements of less than 10 ng/ml because it has been shown that if the total PSA is greater than 10, the PPV is 80%. The cut off value to optimise sensitivity and specificity for prostate cancer detection is dependent on the size of the prostate.[32] A cut off value of percentage free PSA of 23% in a volume below 40 ccs yields 90% sensitivity; to maintain sensitivity in larger prostates, the cut-off value of percentage free PSA should be lowered to 14%. A prospective trial of men aged 50-75 years-old with a PSA of 4-10 ng/ml using a free PSA cut-off level of 25% detected 95% of cancers and 20% of unnecessary biopsies were avoided.[33]

OTHER USES OF PERCENTAGE OF PSA

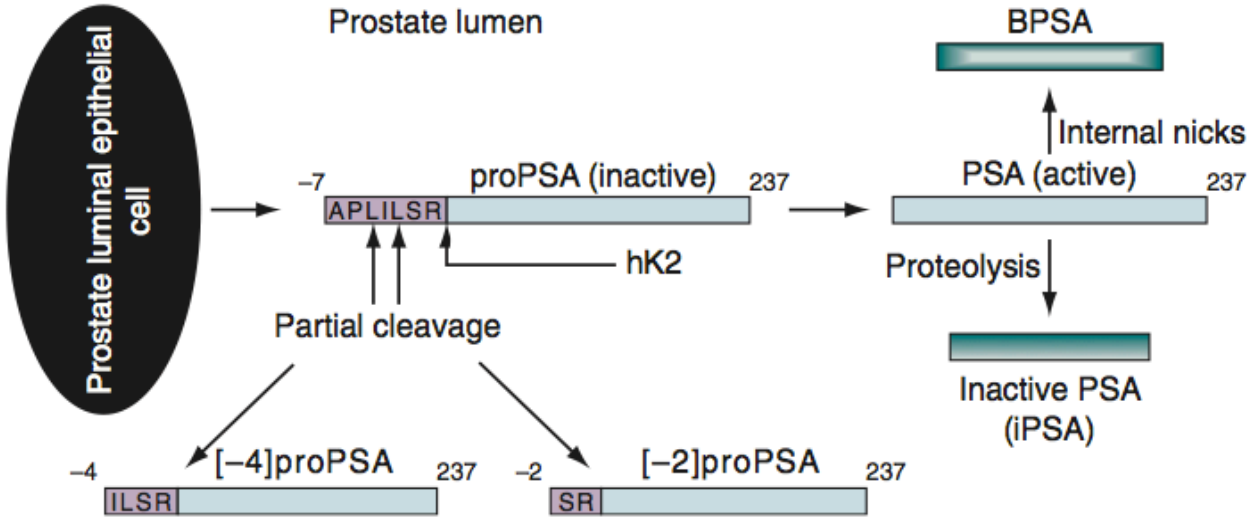
Catalona et al.[34] showed that using a percentage free PSA level of 25%, cancers were detected in 95% of both black and white men suggesting that percentage free PSA can be used independent of race.

Longitudinal measurements of percentage free PSA level using archived serum demonstrates early and significant differences in aggressive and non-aggressive cancers and is often used in active surveillance programmes.[35]

PSA has a number of different isoforms. The prostate luminal epithelial cell produces proPSA which is inactive and is joined by 7 amino acids, then cleaved by the enzyme hK2. If there is complete cleavage, active PSA is produced which is inactivated by proteolysis, producing inactive PSA. The level of inactive PSA is reduced in prostate cancer. When partial cleavage of proPSA occurs [-4] proPSA, [-2] proPSA and [-5] proPSA are produced. This occurs more frequently in cancer cells. A free to total PSA ratio is measured in benign cells by the amount of free PSA in the serum. Free PSA is produced when proPSA is cleaved by hK2 and PSA is produced. PSA is proteolised, producing inactive PSA which diffuses through the basement membrane and is bound to alpha 1-antichymotrypsin. As this occurs, free PSA diffuses into the serum. In a malignant cell the basement membrane is disrupted, therefore a large amount of PSA diffuses and is bound to alpha 1-antichymotrypsin. However, because it has not been cleaved successfully and the proteolytic element is not formed, very little free PSA is formed, and more proPSA is produced (either on its own or as [-5] proPSA and [-2] proPSA).[36]

[-2] proPSA can be used to predict prostate cancer.

Figure 6.PSA derivatives - PSA Isoforms. Campbell's Urology 2012.



The use of percentage pro PSA has been shown to be significantly more accurate in prostate cancer prediction than percentage free PSA. Sokoll et al.[37] found that using percentage proPSA, 75% of cancers were detected, and 59% of unnecessary biopsies were avoided in men with a PSA of 2.5-4 ng/ml. This was much better than the detection rate using percentage free PSA which detected only 33% of unnecessary biopsies.

If PSA level is not used, the alternatives are biomarkers. Several have been developed and tested and may be useful in combination with PSA level. However, this technology is not ready to be used currently.

In conclusion, PSA is widely accepted as a tumour marker and is a low-cost test. It is effectively organ specific although not disease specific. PSA is found in free and complexed forms in the serum and it has been shown that men with prostate cancer have a lower percentage of free PSA. PSA is cleaved to form an inactive precursor of proPSA. proPSA levels can be used to improve the diagnostic yield of prostate cancer and reduce the number of unnecessary biopsies. Is there any role for novel biomarkers?

Enhanced Individualisation Through New Strategies in Castration-Resistant Prostate Cancer (CRPC)

Rodolfo Passalcqua

There are new strategies for enhancing individualisation of care for patients in castration resistant prostate cancer (CRPC).

Patients with distant metastasis have only a 20% probability of surviving for 5 years.[1] The approved first-line treatment for prostate cancer with low-volume metastases and minimal symptoms is with the immunotherapy vaccines Sipuleucel-T and Abiraterone. In prostate cancer with progressive symptomatic metastases the first-line treatment is Docetaxel. High-volume prostate cancer with symptomatic metastases requires second-line treatment with Enzalutamide, Abiraterone, Cabazitaxel and Mitoxantrone. The most important target in treating prostate cancer is the androgen receptor pathway. Androgen deprivation therapy is the first-line therapy for metastatic disease however, response to therapy is temporary and patients invariably progress to CRPC. Despite acquired resistance to androgen deprivation, CRPC continues to depend on androgen receptor signalling for growth. Growth of the prostate cancer cell in

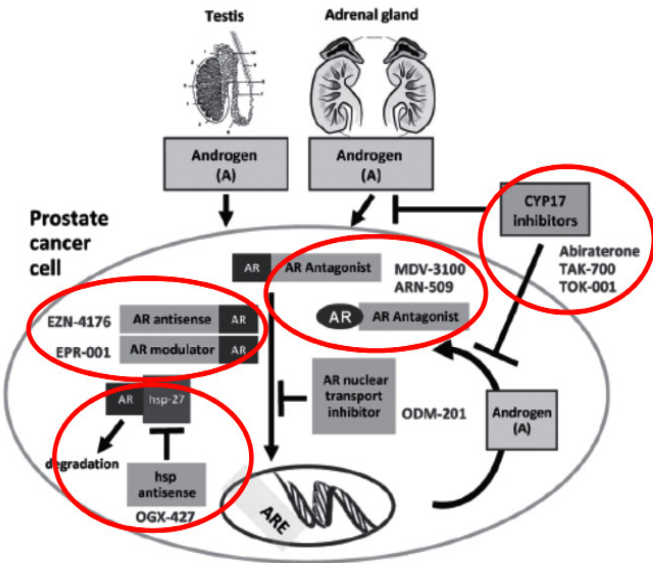


Figure 7: Agents targeting castration-resistant prostate cancer. Leibowitz: Current Oncology. 2012; 19 (3).

the presence of castration can be maintained in different ways, including intra-tumour or adrenal production of androgen (Figure 7). These pathways can be used as a target for new therapies.[38]

Abiraterone and low-dose corticosteroids affect the steroid biosynthesis pathway at the adrenal cortical level; abiraterone and ketoconazole block both the 17a-hydroxylase and the C17-20 lyase enzymes, thus preventing the synthesis of cortisone and the sex hormones. Two new compounds: orteronel and galeterone (currently in Phase III and II clinical development, respectively) target C17-20 lyase specifically, and do not influence the blood concentration of corticosteroids.

In patients with metastatic CRPC who have previously received chemotherapy, abiraterone has been shown to increase the overall survival rate compared with placebo (hazard ratio: 0.65, 95% confidence interval [CI] 0.54 to 0.77, p<0.001).[39] These results led to the registration of abiraterone as second-line treatment of CRPC. Enzalutamide is an oral androgen receptor antagonist that has been tested in two Phase III double blind placebo controlled trial. The trial included CRPC patients pre-treated with docetaxel and the results indicated that the median overall survival rate was 18.4 months (95% CI, 17.3 to not yet reached) in the enzalutamide group compared with 13.6 months (95% CI, 11.3 to 15.8) in the placebo group, showing that enzalutamide significantly prolonged survival in men with metastatic CRPC.[40] A further multinational Phase III randomised double-blind, placebo-controlled efficacy and safety study of

enzalutamide in men with chemotherapy-naive, metastatic castration-resistant prostate cancer (PREVAIL) is in progress. The results are expected soon. More recently, abiraterone was evaluated in a double blind study. The study compared abiraterone + prednisone with placebo + prednisone, in patients with metastatic prostate cancer who had not received chemotherapy. The co-primary end points were radiographic progression-free survival and overall survival. The median radiographic progression-free survival was 16.5 months with abiraterone + prednisone and 8.3 months with prednisone. (HR for abiraterone + prednisone vs. prednisone alone, 0.53, 95% CI, 0.45 to 0.62; P<0.001). Over a median follow-up period of 22.2 months, overall survival was improved with abiraterone + prednisone (median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; P=0.01) but did not cross the efficacy boundary. The results showed that overall progression-free survival was significantly improved in the abiraterone + prednisone group compared with the prednisone + placebo group and a trend towards improved overall survival.[41]

Microtubules are dynamic cytoskeletal proteins responsible for cellular integrity and architecture, mitosis, transport etc. Agents that target microtubules are effective in metastatic CRPC. To date, docetaxel remains the standard first-line treatment for patients with CRPC. However, a new tubulin-binding drug (cabazitaxel) has been developed for CRPCs that are resistant to docetaxel. In the TROPIC trial, cabazitaxel + prednisone was compared with mitoxantrone + prednisone. Median survival was 15.1 months (95% CI, 14.1-16.3) in the cabazitaxel group and 12.7 months (11.6-13.7) in the mitoxantrone group. Median progression-free survival was 2.8 months (95% CI, 2.4-3.0) in the cabazitaxel group and 1.4 months (1.4-1.7) in the mitoxantrone group (HR 0.74, 0.64-0.86, p<0.0001). The results showed that treatment with cabazitaxel + prednisone significantly improved overall survival and progression-free survival in patients with metastatic CRCP whose disease had progressed during or after docetaxel-based therapy.[42] Cabazitaxel is now the standard second-line treatment for CRPC.

Different immunotherapy agents have been tested in prostate cancer. Sipuleucel-T (Provenge) is an autologous cellular immunotherapy agent that has demonstrated prolonged overall survival. The IMPACT study[43] randomised patients to receive sipuleucel-T immunotherapy for CRPC or placebo. Patients treated with sipuleucel-T showed a significantly improved median overall survival compared with patients treated with placebo (25.8 and 21.7 months respectively, p=0.017). Overall survival was not correlated with PSA change.

Ipilimumab is a monoclonal antibody that has been proven to be effective in Phase II trials[44] of prostate cancer; it is also effective against other tumours such as melanoma. Prostvac is a poxviral PSA-targeted vaccine that is in Phase III clinical development.[45] The vaccine has the potential to significantly improve overall survival in metastatic CRPC.

Approximately 90% of patients with CRPC have detectable bone metastasis.[46] Therefore, bone-targeted therapies are invaluable. In normal bone physiology, the role of the receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL) is crucial because is the central regulator of osteoclast differentiation, activity and survival. In a Phase III study, denosumab (a human monoclonal antibody directed against RANKL) was compared with zoledronic acid for the prevention of skeletal-related events in men with bone metastases from CRPC. The median time to first on-study skeletal-related event was 20•7 months (95% CI, 18•8-24•9) in the denosumab group, compared with 17•1 months (15•0-19•4) in the zoledronic acid group (hazard ratio 0•82, 95% CI, 0•71-0•95; p=0•0002 for non-inferiority; p=0•008 for superiority).[47] This study showed that denosumab was significantly better than zoledronic acid in the prevention of skeletal-related events in men with bone metastases from CRPC.

Radium-223 (Alpharadin) is a new alpha-emitter for the treatment of bone-metastatic CRPC. The ability of alpha particles to travel a short distance from the site of origin and their highly destructive cellular effects, results in the maximum amount of cellular killing and a minimal amount of damage to other tissues. Therefore, radium-223 is highly targeted and localises specifically to the osteoblastic lesions typical of metastatic prostate cancer.[48] In the ALSYMPCA phase III trial[49] (unpublished), radium-223 was shown to improve overall survival compared with placebo.

There are many new promising targeted therapies for the treatment of CRPC. Tasquinimod is a novel small-molecule inhibitor that targets the tumour microenvironment with immunomodulatory, anti-angiogenic and anti-metastatic proprieties.[51,52,53,54] Tasquinimod binds to the S100A9 protein, an immunomodulatory protein expressed on regulatory myeloid cells (also called MDSCs). It has been shown that MDSC can facilitate tumour growth by their ability to down regulate the immune response against

	Progression free survival (months)		P value	HR	CI 95%
	Tasquinimod	Placebo			
Visceral metastases	6.0	3.0	0.045	0.41	0.16-1.02
Bone metastases with or without nodal metastases	8.8	3.4	0.019	0.56	0.34-0.92
Bone metastases only at baseline	12.1	5.4	0.016	0.45	0.23-0.88
Lymph node metastases	6.1	3.1	0.54	0.73	0.27-2.00

Table 2. Median progression-free survival values for tasquinimod versus placebo

cancer cells and to promote neovascularization in tumours. MDSC in the tumour microenvironment participates in the establishment of the pre-metastatic niches. It has been shown that tasquinimod controls the accumulation of MDSC.[51,52,53,54] Tasquinimod inhibits the direct interaction with S100A9 and the receptor for advanced glycosylation end product (RAGE) and toll-like receptor 4 (TLR4) in tumours, both of which promote tumour development though the activation of the intracellular signalling pathways.[51,55,56,57] A Phase II study of tasquinimod in metastatic CRPC, evaluated patients with histologically confirmed prostate adenocarcinoma that were chemotherapy naive and had minimally symptomatic disease. 206 patients were randomised to receive tasquinimod or placebo; the primary endpoint was the progression-free proportion of patients at 6 months. 69% of the tasquinimod-treated patients were progression-free at 6 months compared with 37% of those receiving placebo, this was a statistically significant difference (RR 0.49; 95% CI.36-0.67; p<0.001). The treatment was well tolerated and the majority of patients discontinuing due to adverse events presented grade 1 to 2 toxicities. Median progression-free survival values for tasquinimod versus placebo in the overall population were 7.6 months versus 3.3 months respectively (HR 0.57, 95% CI 0.390.85, p=0.0042). In addition, tasquinimod versus placebo was measured in the following populations: visceral metastases; bone metastases with or without nodal metastases; bone metastases only at baseline and lymph node metastases (Table 2).

PSA level was not correlated with the clinical efficacy of tasquinimod.[58] On the basis of these results, a Phase III trial was conducted in 1,200 patients with a histologically confirmed diagnosis of adenocarcinoma of the prostate who were chemotherapy-naive and were asymptomatic or moderately symptomatic CRPC patients. The primary endpoint is progression-free survival in patients who received tasquinimod compared with placebo and overall survival is a key secondary endpoint. The results of the study have not yet been published.[59]

Cabozantinib is a new multikinase inhibitor that produces dual inhibition of mesenchymal epithelial transition factor (MET) and VEGFR2. In a placebo controlled trial, cabozantinib produced a significant increase in progression-free survival in patients with CRPC. The median progression free survival was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) in the cabozantinib arm compared with 5.9 weeks (95% CI, 5.4 to 6.6 weeks) in the placebo arm. Sequential whole-body technetium methylene di-phosphonate bone scintigraphy of the study population showed multiple areas of increased radiotracer uptake, indicative of extensive bone metastases. Following treatment with cabozantinib the bone scans indicated complete or partial resolution of bone metastases, the result of the bone scan correlated with partial response of tumour lesions in soft tissue and pain relief in each patient.[60]

Another interesting pathway is the PI3K/Akt/mTOR pathway. This pathway is important because there is a crosslink with androgen receptor signalling. Alteration of the PI3K/Akt/mTOR pathway is beneficial in metastatic prostate cancer but not in primary prostate cancer.[61]

Apoptosis and the cytochrome chaperone molecules is another new, interesting target in prostate cancer treatment. This is a complex mechanism involving HSP27, which is an ATP-independent chaperone protein that confers protection against apoptosis through various mechanisms, including a direct interaction with cytochrome and in clustering, which

increases the cell survival by the inhibition of general cellular stress and the transcriptional induction of survival genes. HSP27 inhibits apoptosis by integrating different pathways, including intrinsic and extrinsic apoptosis and pro-factor pathways. OGX427 is an anti-nucleotide that acts at each critical point by reducing HSP27 levels. Trials with agents targeting cytoprotective chaperone proteins in metastatic CRPC are in progress and beginning to show promising results.[62]

Poly ADP-ribose polymerase (PARP) is a protein that plays a critical role in androgen receptor activity. PARP1 activity is enhanced in advance disease, and promotes androgen receptor residence on chromatin, androgen receptor dependent tumour growth, and castration resistance. Ablation of PARP1 activity improves the response of androgen receptor therapy for locally advanced prostate cancer.

New agents that target androgen receptors are also being investigated in Phase I and II clinical trials. These include ARN-509 (an androgen receptor antagonist), ODM-201 (which blocks androgen receptor nuclear translocation), EZN-4176 (an androgen receptor antisense nucleotide that attacks the mRNA of an androgen receptor), and EPR-001 (a small molecule that blocks the activation of androgen receptors).

In summary, the Phase III published studies show that in metastatic CRPC, the demonstrated overall survival remains a challenge. However, the landscape of the management metastatic CRPC is rapidly changing. New first-line treatments are becoming available to patients with low-volume metastases, including treatments with reduced toxicity that will increase survival, delay chemotherapy treatment, and improve quality of life. Sequencing agents in metastatic CRPC present the possibility of personalised treatment. Androgen deprivation therapy should be maintained for all patients and there is a wide range of new treatments that promote androgen deprivation including androgen targeting inhibitors or androgen synthesis inhibitors (abiraterone and enzalutamide), immunotherapy (sipuleucel-T) and new agents that are under investigation (such as, tasquinimod and other androgen receptor targeting treatments). When patients become symptomatic and/or there is a rapid progression rate, chemotherapy with docetaxel is the first option followed by sequencing agents (docetaxel re-challenge, cabaxitaxel, mitoxantrone, abiraterone, enzalutamide, radium 223). However, the scope of combining different drugs with different mechanisms of action is infinite - the future of treating CRPC will be a new and exciting period.

Treatment of Individualisation up to Patient Support

Peter Hammerer

There are many drugs available to treat prostate cancer, however the optimal sequence is yet to be defined. The pathology of breast cancer illustrates the importance of genomic portraits in cancer treatment. What can be learned from rectal cancer?

In colorectal cancer, the genes KRAS and BRAF play a major role in mutational status test analysis and result reporting. A study on the impact of KRAS mutations on response to EGFR-targeted therapies in colorectal cancer has shown that if KRAS status is positive, progression-free and overall survival is poor, and if KRAS status is negative the progression-free and overall survival rate improves.[63] This also occurs in lung cancer.

In prostate cancer, there are 4 areas where an individualised approach to treatment is required; decision to diagnose, treatment for low-risk prostate cancer, treatment for high-risk prostate cancer and treatment for CRPC. Risk calculators can assist in making decisions regarding diagnosis and treatment, for example the PCPT risk calculator[64] calculates the patient's estimated risk of biopsy-detectable prostate cancer and therefore indicates the need for biopsy. However, it is clear that one standard treatment for prostate cancer does not fit all patients and that there are anomalies surrounding detection and treatment methods:

The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines version 1.2013[65] demonstrate that in low-risk prostate cancer (T1-T2a with a Gleason score of ≤6 and low PSA less than 10 ng/ml) there are different options for treatment, depending on life expectancy. In low risk disease if life expectancy is less than 10 years, active surveillance is the treatment of choice. Active surveillance is described as PSA test at least as often as every 6 months and digital rectal examination at least as often as every 12 months. If life expectancy is 10 years or more, treatment is recommended as follows: active surveillance (defined as PSA test at least as often as every 6 months, digital rectal examination at least as often as every 12 months and a repeat prostate biopsy as often as every 12 months), radiotherapy (daily IGRT

with IMRT/3D-CRT) or brachytherapy or surgery (radical prostatectomy, ± pelvic lymph node dissection if the predicted probability of lymph node metastasis is ≥2%).

However, it is recognised that at present active surveillance could be improved, this is illustrated by the 'Johns Hopkins Experience' which assessed 769 men enrolled in an active surveillance program for prostate cancer. The results showed that the number of patients who were intervention free after 10 years was only 41%. 255 of the 769 men (33.2%) had an intervention, and of those 255 men, 188 (73.7%) men had intervention due to a biopsy result.[66] However, there are nomograms available to predict minimal prostate cancer for patients selecting active surveillance,[67] and the results of the nomogram may help to select patients for active surveillance.

Another method of detecting cancer is imaging, e.g. histoscanning, but although there are many papers discussing histoscanning, there are no large clinical trials to validate this method of detecting prostate cancer. However, magnetic resonance imaging (MRI) can help to identify a lesion[68] and assist in determining treatment. Multiparametric MRI is required for prostate cancer detection, and this includes T1 and T2 weighted images, dynamic contrast, diffusion weighting and proton spectroscopy. Although it has been shown that T2 weighted images for prostate cancer vary considerably in sensitivity (37% to 96%) and specificity (21% to 87%),[69,70] the variability of MRI is observed frequently in clinical practice because scoring and reporting systems differ significantly. For the diagnosis of prostate cancer it is essential that MRI scanning is standardised to ensure that there is improved detection and subsequent treatment of prostate cancer.

The stratification of treatment of prostate cancer is based on life expectancy but there is no standard method of calculating life expectancy in prostate cancer patients. However, there are several life expectancy calculators available on the internet that estimate how long someone is expected to live when they reach a specific age. The use of this type of uniform document to calculate life expectancy enables consistent stratification on which treatment can be based.

The benefit of surgery is estimated according to the Gleason score and patient age. Vickers et al. studied individualised estimations of the benefit of radical prostatectomy and found that the benefit of surgery varied widely depending on age and tumour characteristics, reporting that at 65 years-old the absolute 10 year risk reduction in prostate cancer mortality of radical prostatectomy ranged from 4.5% in low risk patients to 17.2% in high risk patients. They concluded that treatment is more of a 'judgement call', based on patient preference and other clinical findings.[71]

A patient at high risk with a positive margin who has had surgery may need additional adjuvant treatment such as radiation therapy or hormone treatment, there is no clearly defined 'next step' following surgery. Trials are required to identify adjuvant treatment following prostatectomy.

There are new strategies in prostate cancer which will improve diagnosis and treatment, for example genomics. Following biopsy, next generation sequencing (NGS) detection of 'driver' mutations may help to identify men who are the most suitable candidates for active surveillance, surgery or radiation therapy. In metastatic prostate cancer, NGS detection of 'driver' mutations may also help to select targeted therapy, especially when the cancer is resistant to normal hormone treatment.[72]

In conclusion, the concept of 'one-size-fits-all' is less relevant for the future. Individualised treatment is possible, based on patient preference, biomarkers, and genomic alterations. Urologists can learn from experts in breast cancer; it is important that a multidisciplinary approach is incorporated into the treatment of prostate cancer, to ensure optimal treatment for this group of patients.

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Transurethral Resection of Bladder Tumour: How to Reach Excellence

Summary of Presentations given at the Ipsen Satellite Symposium 28th Annual EAU Congress, 15-19 March 2013

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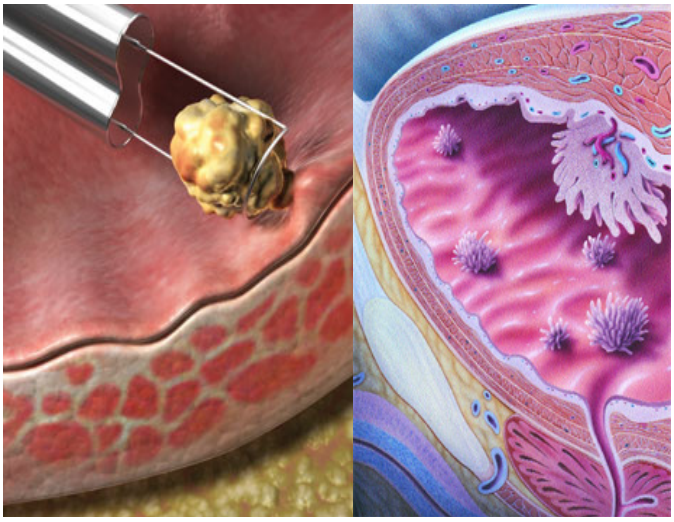
Transurethral Resection of Bladder Tumour: How to Reach Excellence

Maurizio Brausi

The aim of this symposium was to review the new 'tools' available for the diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC).

Trans-Urethral resection of Bladder Tumour (TURBT) under white light is considered the gold standard for the diagnosis and treatment of bladder tumours. Transurethral resection (TUR) is one of the most frequent and important operations performed by urologists for the diagnosis and treatment of TURBT; it is estimated that more than 700,000 are performed in Europe each year.[1]

Figure 1: Transurethral resection of Bladder Tumour (TURBT)



The goal of an adequate TURB is the removal of all visible tumour and the performance of accurate tumour staging. To correctly assess staging, the presence of detrusor muscle (DM) in the resected specimen is required. Tumour extension must be assessed, with biopsies in the adjacent areas, random areas and prostatic urethra. There should be no bladder perforation and good haemostasis should be obtained.

The quality of the TURB is determined by good pathological evaluation. This is dependent on the specimen containing DM. The pathologist assists the urologist by providing comprehensive details of the extent of the tumour. This includes details on the extent of the invasion of the basal membrane, lamina propria and muscle, the degree of vascular or lymphatic invasion, an assessment of the presence of concomitant carcinoma in situ (CIS), and provision of the tumour grade.

There are clinical and pathological parameters that define an adequate TURB. They are: (1) the 3 month recurrence rate. (2) The rate of patients with detrusor muscle (DM) in the resected specimen. (3) The detection rate of CIS. (4) The complication rate.

However, there is room for improvement in the operative performance of TURBTs. This is illustrated by the fact that in standard practice, tumour recurrence rate is between 46–48%, and only 50–60% of specimens contain DM, resulting in the invasiveness of the tumour not being evaluated in at least 40% of patients. These

patients are staged as 'tumour not visible but proven' or 'cannot be assessed' (Tx). In centres of excellence, the complication rate is 4%, and includes bleeding, bladder perforation, and revision of operation. In addition, the detection rate of CIS is only 5–10%.[2]

Can We Improve?

The following sections describe methods to improve the TURBT technique, including new technologies that may help to improve results, new treatment approaches, and the cost implications of the new technologies.

Improving Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer

Fred Witjes

There are still some challenges in the diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC). Improvements can be made to reach excellence, including improved diagnosis, improved TURBT, reduced recurrences, and decreased progression.

Improved Diagnosis in Bladder Cancer

Bladder cancer is currently diagnosed using cystoscopy, urinary cytology, and urinary markers, but there are some problems with the efficacy of these diagnostic techniques.

Cystoscopy is a frequently performed procedure, and is the only proven procedure assigned Level 1 evidence in the new EAU guidelines.[2] However, using cystoscopy up to 40–45% of papillary bladder tumours are not detected,[4] which is important because CIS is an aggressive disease that should not be overlooked. Integrated results from photodynamic diagnosis (PDD) studies show that 62% of CIS lesions are not detected when white light (WL) cystoscopy is used, and in 29% of patients the CIS is not detected at all.[5] This can be resolved by carrying out a re-TUR, and indeed positive re-TUR rates are around 50%, indicating that at first resection, part of the tumour had not been removed.[4]

The use of urinary cytology in the diagnosis of NMIBC is subjective it has high inter- and intra-observer variability. Urinary cytology has a high specificity but a low sensitivity and is ineffectual in cases of infection or during intravesical therapy. Although urinary marker sensitivity is higher than cytology sensitivity this technique alone is insufficient in the diagnosis of NMBIC. To date, there is no urinary marker that can assist in the diagnosis of bladder cancer. Evidence shows that there are no markers or cytology that can replace cystoscopy.[6] Therefore, cystoscopy remains one of the most important techniques in the diagnosis of bladder cancer.

Improved TURBT in Bladder Cancer

The 2013 EAU guidelines[3] explicitly describe how a good urethral cystoscopy and TURBT should be performed; in addition the guidelines describe how and when biopsies should be taken. New studies support the guidelines, and show the importance of an effective and complete TUR for diagnosis and prognosis of the patient. For example, in a study of 473 patients, Mariappan et al. (2012)[7] found that only 69.6% of patients who underwent complete TURBT had DM present in NMIBC specimens. Their findings stressed that an effective and complete TUR must contain DM. These results suggest that there is room for improvement in the performance of TURBT to obtain an effective and complete result.

It is clear that the diagnosis and prognosis of patients with bladder cancer should be improved. There are several ways that improvements can be made. Firstly, a re-TUR can be done - the EAU guidelines[3] recommend a second TURBT after 2-6 weeks if the initial TUR is incomplete, if there is no DM in the specimen (with the exception of Ta G1 tumours) and in all initial T1 or G3 tumours (except primary CIS). Secondly, a dedicated teaching programme for residents and staff has been shown to increase the number of complete and effective TURs[8], which translates into less recurrence, more DM present in the specimens and less complications (such as perforation and bleeding) and an improved outcome for the patients. Thirdly, TURs are often planned at the end of the operating schedule due to the perception that they can be done quickly; this perception is false. TUR is a real operation that deserves attention and training. Another method of improving results is by acknowledging that sometimes visual acuity is deficient and needs to be perfected. One way of doing this is to use fluorescence techniques for PDD. Studies using 5-aminolevulinic acid (5-ALA) have shown that more tumours can be detected,[9] there is 20% less residual tumour after TURB with 5-ALA,[10-12] and the long term recurrence rate is lower.[12-14] Similarly, the use of hexaminolevulinate (HAL), which is the only registered compound, has shown a higher detection rate of up to 25%,[15-18] improved patient management of up to 20%,[19] and lower early and late recurrence rates.[20-21] When compared with 5-ALA, HAL has a reduced instillation time and better colour contrast.[22] A systematic review of 17 trials using PDD showed that 20% more patients with NMIBC were detected, 39% more patients with CIS were

detected, there was less residual tumour (OR: 0.28), and statistically significantly higher recurrence-free survival than WL cystoscopy (p=0.0002).[5]

Furthermore, a new method; Narrow Band Imaging (NBI) also improves visualisation. NBI it is an optical image enhancement technology that improves the visibility of blood vessels and other structures on the bladder mucosa using two specific wavelengths that are strongly absorbed by haemoglobin. The advantages of NBI are that it is easily available, can be used in the outpatient setting, has an improved detection rate, and a lower recurrence rate.[23] The disadvantages of NBI are that it looks at vascularisation which is not tumour specific, and additional equipment, software, and lenses are required. The data on the use of NBI are very limited, in particular there are no data on CIS detection using NBI, therefore more information is required to assess its use in the diagnosis of bladder cancer.

Reduced Recurrences

Urologists are hindered in reducing the recurrence rate by insufficient diagnosis, limited efficacy, and old drugs (the last new registered drug for instillation therapy was Bacillus Calmette-Guérin [BCG] in the eighties). New drugs are being researched but are not available at present. In addition, there is insufficient discrimination between patients receiving therapy. 'Tailored therapy', e.g. an assessment of the need for, and response to adjuvant therapy, would reduce recurrence rates, but new markers are required for this to become a reality.

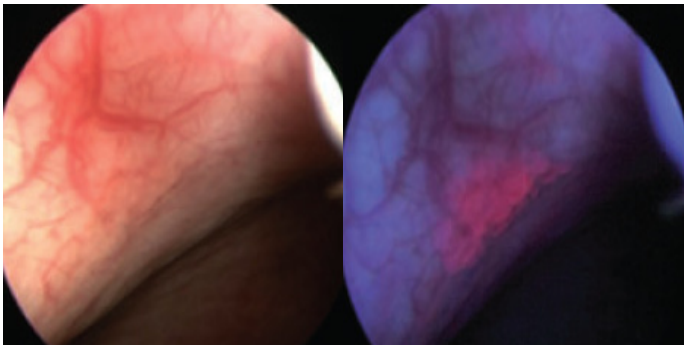
Less Progression

There is on-going discussion regarding the efficacy of BCG in reducing progression of NMIBC. An individual patient meta-analysis[24] involving approximately 3, 000 patients evaluated the long-term outcome of randomised studies comparing intravesical mitomycin C and BCG for NMIBC. The meta-analysis found that in 1,880 patients 12% of the patients progressed and 24% died (of those 30% due to bladder cancer). No statistically significant differences were found for the long term endpoints, indicating that BCG had no influence on the endpoints, and that at best the impact of BCG on progression is limited.

There is one final general problem in improving diagnosis and treatment of NMIBC, and that is that urologists are relatively stubborn! It has been shown that urologists don't always comply with the guidelines: a study of 4,545 patients with high-grade NMIBC showed that only 1 patient received all the recommended diagnostic, treatment and follow up measures.[25] This could certainly be improved if the guidelines were followed.

To achieve excellence in the diagnosis and treatment of NMIBC the following points should be considered. The diagnosis of NMIBC is usually made using WL cystoscopy, which does not detect all lesions. The use of cytology for diagnosis has limited value; there are no markers to assist with analysis, and although genomics are being developed they are not currently available. The most important aspect of the treatment of NMIBC is a good TUR. Clinically this can be significantly improved by using PDD, which means a much better outcome for the patient. Instillation therapy using mitomycin C or BCG is adequate but could be improved. Unfortunately, recurrence and progression rates remain problematic; and therefore it is essential that urologists follow the guidelines for the diagnosis and treatment of NMIBC to achieve excellent clinical and patient outcomes.

Figure 2: Hexaminolevulinate (HAL) compared to 5-aminolevulinic acid (5-ALA). Geavlete 2011.



Reviewing the Data: The Hexaminolevulinate-Guided Blue-Light Cystoscopy Meta-Analysis

Maximilian Burger

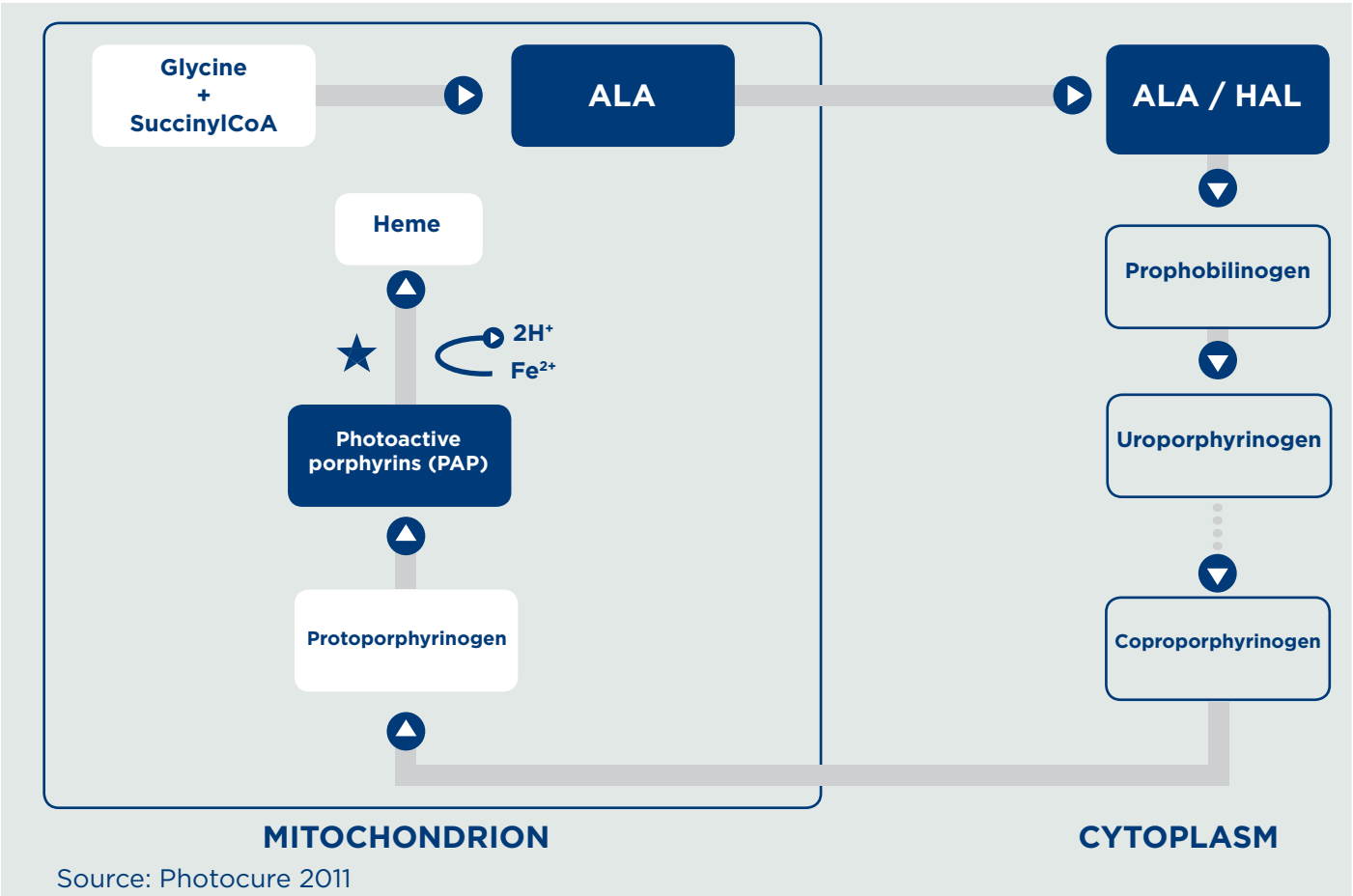
White light (WL) cystoscopy is commonly used in the diagnosis and treatment of bladder cancer. However, flat tumours maybe not be detected when using WL cystoscopy. In addition CIS, multifocal growth, and microscopic lesions can be overlooked or inadequately resected. Residual tumour or growth of undetected lesions may account for many cases of early recurrence.

Blue-light (BL) cystoscopy improves the visual demarcation between normal and malignant tissue. This is because the photoactive agents used accumulate preferentially in neoplastic tissue. It is not fully understood why this happens but it is known that there is a different level of enzymes in neoplastic tissue compared with benign tissue, the agents degrade at different rates and therefore preferential accumulation can be induced in neoplastic tissue. Illumination with blue-violet light (375nm–440nm) results in a clearly demarcated red fluorescence from malignant tissue.

Hexaminolevulinate (HAL) is the hexyl ester of 5-ALA and is the only photoactive agent that has been approved in the detection of bladder cancer. The use of blue-violet light and HAL in BL cystoscopy provides a considerable advantage in the identification of malignant tissue compared with WL cystoscopy. However, the optical instruments are complicated and require some financial investment.

There are conflicting opinions regarding the use of BL cystoscopy. There are numerous well-conducted studies that confirm that BL cystoscopy with HAL improves the detection of tumours[15,16,19,26] and the EAU guidelines 2012[27] report an additional 20% detection rate for papillary tumours and 23% for CIS using BL cystoscopy with HAL. Conversely, the EAU guidelines 2011[27] on NMIBC conclude 'that the value of fluorescence cystoscopy for improvement of outcome in relation to progression rate or survival remains to be demonstrated', however the studies used in this analysis report different outcomes. Published meta-analyses on PDD do not agree on the effect on recurrence; Kausch 2010[5] reports that 'data indicate at evidence levels 1 and 2 that PDD detects significantly more tumour-positive patients than white light cystoscopy alone, PDD reduces residual tumour rates and increases tumour-free survival significantly (evidence level 1)'. Shen et al 2012[28] reports conflicting results: 'fluorescence-guided TURBT was not superior to conventional white light in diagnostic accuracy. Even though fluorescence-guided TURBT had an advantage in reducing tumour rates, it had no significant effect on short-term recurrence-free survival and progression-free survival'. The limitations of both meta-analyses were that combined data were used for the two agents, HAL and 5-ALA.

Figure 3: Heme Biosynthetic Pathway



Source: Photocure 2011

The limitations observed in the previous studies prompted a new meta-analysis on HAL cystoscopy in NMIBC to provide raw individual patient data in the analysis to improve statistical accuracy focussing on only one agent (HAL). HAL is the only photoactive agent approved by the European and US regulatory authorities for the detection of bladder cancer, therefore a separate meta-analysis of the effects of HAL-assisted BL cystoscopy was warranted.

The meta-analysis evaluated only well-controlled studies that used HAL as indicated as an adjunct to WL cystoscopy. The aim was to detect the rate of papillary (Ta/T1) and flat (CIS) tumours and the impact on tumour recurrence. Intention to treat (ITT) populations were used for detection and the per protocol (PP) populations for recurrence, sub-group analyses were carried out on initial and recurrent cancer patients in high, intermediate, and low risk groups. The statistical analysis methods were selected to minimise the effects of heterogeneity of the data. The meta-analysis identified 8 studies. Eligibility criteria were: that the study was prospective, recruited patients with known or suspected NMIBC (Ta, T1, or CIS) diagnosed by cystoscopy or positive urine cytology, or indicated by their medical history; the study compared a single application of HAL with BL and WL cystoscopy either in randomised control groups or within-patient comparison; reported detection by lesion type and WL and BL separately; carried out HAL cystoscopy according to recommended instructions, and used histology to confirm the nature of lesions. PubMed and the Cochrane Library were searched in July 2011 for controlled trials of PDD with HAL. No restrictions on language or date were set.

The database searches revealed 122 publications, 104 were immediately rejected as irrelevant on the basis of titles or abstracts, 8 papers were rejected because they did not meet the inclusion criteria, leaving 10 for inclusion. One group[29-30] was unable to provide raw data, therefore 8 studies (9 papers) were analysed. All of the studies except 1 (Hermann 2011, which was excluded) compared WL cystoscopy alone with both WL plus BL cystoscopy, using PDD equipment from KARL STORZ, as within-patient comparison before carrying out TURBT. This enabled documentation of lesions that could be detected with both methods, with BL only, or with WL only. In total 1293 patients received HAL.

The results showed that PDD with HAL detected significantly more Ta, T1, and CIS tumours than WL cystoscopy. 5 studies reported additional detection of Ta tumours with BL cystoscopy, ranging from 9.7% to 19.4% of the total Ta tumours detected A total of 202/1529 (13.2%) additional Ta tumours were detected using BL cystoscopy alone. In all studies except 1, the additional detection rate of Ta tumours was highly significant ($p<0.001$, risk ratio [RR] 2.136 in favour of BL cystoscopy; CI: 1.578–2.890). 5 studies

Table 1: Meta-analysis of 1293 patients receiving HAL

Study	Patients	Design	Detection/ Recurrence
Schmidbauer 2004	211	Within patient comparison, WL then BL	D
Grossman 2007, Fradet 2007	196	Within patient comparison, WL then BL	D
Jocham 2005	146	Within patient comparison, WL then BL	D
Stenzl 2010	365	Detection: within patient comparison, WL then BL Comparison of randomized parallel groups. Recurrence: Group 1 vs Group 2	D, R 9 months
Hermann 2011	n/1	Comparison of randomized parallel groups. Detection and recurrence: Group 1 vs group 2	D, R
Burgués 2011	308*	Within patient comparison, WL then BL	D
Drăgoescu 2011	42	Comparison of randomized, parallel groups	D, R
Ray 2009	45*	Within patient comparison, WL then BL	D
Total	1293		

*Additional patients for analysis were provided by some authors

reported detection of additional T1 tumours, ranging from 3.6% to 12.5% of the total T1 tumours detected. A total of 34/361 (9.4%) additional T1 tumours were detected with BL cystoscopy (p=0.068, RR: 1.807; CI: 0.957–3.412). 5 studies reported detection of additional CIS lesions ranging from 31.9% to 50.5% of the total CIS lesions detected. Overall, 203/510 (39.8%) additional CIS lesions were detected with BL cystoscopy alone. This additional detection rate of CIS was highly significant in all studies (p<0.001; RR: 10.949; CI: 6.808–17.610) .[15-16,19,26,31-34]

Not all sub-groups showed significant benefit. However, in Ta patient groups with primary tumours favourable results using BL cystoscopy were seen (RR: 3.992; CI: 1.833–7.040), and slightly less recurrence (RR: 1.970; CI: 1.399–2.775) was observed. Significant benefit was observed using BL in both the Ta high risk group (RR: 1.867; CI: 1.186–2.939; p=0.007) and intermediate risk group (RR: 3.132; CI: 1.992–4.926; p<0.001), but not in the low risk group (RR: 0.702; CI: 0.244–2.021; p=0.512). In the group of T1 patients, improvement was seen in diagnosing initial cancer (RR: 3.978; CI: 1.617–9.785; p=0.003) but not in recurrent cancer. In the CIS group, highly significant increases were shown in the diagnosis of initial and recurrent cancers: initial cancer (RR: 20.651; p<0.001; CI: 7.766–54.909) and recurrent cancer (RR: 7.581; CI: 4.364–13.168; p<0.001).

HAL cystoscopy also detected significantly more patients with Ta and T1 tumours. There were 168/790 (21.3%) patients who had at least one additional Ta or T1 tumour that was only identified by BL cystoscopy, (event rate 0.217; CI: 0.139–0.247; p<0.001). Similarly, in patients with primary tumours, additional Ta or T1 tumours were identified by BL cystoscopy in 58/346 (16.8%) patients (event rate 0.173; CI: 0.123–0.239; p<0.001), and in high risk Ta and T1 groups, 83/377 (22.0%) of patients with additional tumours were identified by BL only (p<0.001). In the intermediate risk Ta tumours sub-group, 79/237 (33.3%) of patients were identified with additional tumours (p<0.001); and in the low risk Ta tumour sub-group, an additional 6/176 (7.9%) patients were identified (p<0.001).

There were 61/256 (23.8%) patients who had at least one CIS lesion that was identified only with BL cystoscopy; in these patients, no CIS lesions had been identified by WL cystoscopy. Additional CIS lesions were found only by BL cystoscopy in 30/110 (27.3%) patients with initial cancer (event rate 0.283; CI: 0.205–0.378; p<0.001), and in 31/146 (21.2%) of patients with recurrent cancer (event rate 0.218; CI: 0.158–0.294; p<0.001).

The detection results showed that overall, HAL cystoscopy detects a statistically significant number of additional Ta, T1, and CIS lesions. HAL cystoscopy identified 24% of patients with CIS when none were seen in WL cystoscopy.

Recurrence was analysed in 3 studies (634 patients total) with parallel groups;[26,31,34] in all 3 studies, HAL BL cystoscopy was associated with a lower rate of recurrence. For this analysis PP populations were used as these give a truer picture of recurrence, and the ITT populations included imputed data on recurrence when patients were lost to follow up. The difference in overall recurrence rates was 34.5% for WL and 45.4% for BL, which is statistically significant in favour of BL cystoscopy, (p= 0.006). This gives a significant relative reduction of 24% in the recurrence rate following BL cystoscopy at 12 months (RR=0.761, [0.627-0.924]; p=0.006). Recurrence rates were even lower following BL cystoscopy in the sub-groups of patients with T1 or CIS, the difference in recurrence rate was 16.6% (RR: 0.696; CI: 0.482–1.003; p=0.052). In the Ta sub-group, RRs indicate a reduction in risk despite borderline statistical significance (RR: 0.804; CI: 0.653–0.991; p=0.040).

In conclusion, the meta-analysis showed a single application of HAL cystoscopy detects a significant number of additional lesions in patients with suspected bladder cancer, and reduces recurrence rates for up to 1 year. Importantly, HAL BL cystoscopy identified CIS not seen after inspection with WL cystoscopy. Increased detection rates were seen in all sub-groups, and a reduction in recurrence rates were seen in high and low risk Ta patients as well as T1 and CIS patients. In addition, the analysis showed that detection of additional lesions can reduce the overall risk of recurrence and significantly change the patient management plan. These findings are supported by other studies that have shown that a single application of HAL cystoscopy has beneficial effects on recurrence rates extending up to 5 years.[21]

Blue-Light and Management of Non-Muscle Invasive Bladder Cancer: Cost-Effective Analysis

Fred Witjes

In terms of cost-effectiveness, it's worth bearing in mind that a small investment can be cost effective, whereas low-cost is not always 'value for money'. Bladder cancer is the fifth most expensive cancer in terms of total medical care costs. Per patient cost from diagnosis to death amount to between 96,000 and 187,000 US dollars (2001 values). Current diagnostic procedures, therapies, and conventional frequent follow ups are not cost effective, and there are no new developments in pharmaceutical treatments and other technologies.[35]

Urologists have a vital role in the treatment of patients with bladder cancer. The estimated number of TUR procedures performed in 2011 in the US was 370,000, and 750,000 in the EU. Some patients are seen in outpatient departments where coagulations are performed, and when these patients are included in the prevalence estimate, 570,000 patients in the US, and >1,000,000 patients in the EU were treated for bladder cancer in 2011. This illustrates the enormous tumour treatment burden for urologists. The 2011 estimate for instillation therapies was close to 3,000,000 in the US, and almost 6,000,000 in EU. These figures indicate that bladder cancer deserves more attention.

Two out of three bladder cancer costs are related to TURBT for NMIBC as opposed to other diagnostic methods such as CT scans etc. The costs vs. benefit of bladder cancer treatment and follow up differ significantly per country and healthcare system.[36] Therefore, cost calculations should only be done on individual healthcare systems.

Table 2: Cancer incidence and prevalence

Tumour	Incidence US 2005	Incidence EU 2004	2008 World Incidence
Bladder ca	63,210	120,000	
Bladder ca estimates	2008: 68,810 2013: 73,570	149,000	382,660
Colon ca	145,290	376,400	
Lung ca	172,570	381,500	
Prostate ca	232,090	237,800	
Breast ca	211,240	370,100	

Department of Urology

The costs for using BL cystoscopy include the light source, dedicated optics, the light cable, the camera, and the compound (Hexvix®). The non-equipment related costs include the catheter for Hexvix instillation, doctor/nurse, administration, anaesthesia time, pharmacy, and pathology. The total extra cost of BL TURB per case of non-equipment related costs in Germany[37] is €584.21, which is apportioned as follows: €47.71 for the operating room (which includes the extra operating time required to perform BL cystoscopy), €522.80 for the drug and instillation, and €3.70 for administration etc. It has been proven in numerous trials that BL cystoscopy improves care and detects more lesions. BL-TUR results in improved complete resection rates, less residual disease, and an improvement in the number of complete diagnoses made. Improved diagnosis leads to improved additional therapy, and consequently in fewer recurrences and fewer TURBTs. If there are fewer non-identified lesions, a reduced number of subsequent radical treatments are required.

Studies in different countries with different health care systems have shown that there is some potential to save money by using BL cystoscopy. Burger et al. (2007)[38] reported the cost effectiveness of BL cystoscopy compared with WL cystoscopy, using 5-ALA, in Germany. The study involved 301 randomised patients who were followed up at 7.1 years, and found that the total recurrence rate was 18% with BL cystoscopy compared with 42% with WL cystoscopy. Per patient there were 0.3 recurrences with BL cystoscopy compared with 1.0 using WL cystoscopy. Additionally, TUR rates were less using BL cystoscopy, 0.8 compared with 2.0 using WL cystoscopy. The total cost per patient was €420 using BL cystoscopy compared with €1,750 using WL

Table 3: Average European BC treatment reimbursement (procedure and hospital stay inclusive). Sievert et al. W J Urol 2009

	UK in £ ($)	Germany in € ($)	France in € ($)	Italy in € ($)	Belgium in € ($)
Cystoscopy	**422 (620)**	46 (61)	**38 (51)**	57 (76)	40 (53)
TURB	1,465 (2,154)	**2,231 (2,967)**	**845 (1,124)**	2,061 (2,741)	1,655 (2,201)
Cystectomy	**3,867 (5,684)**	**15,419 (20,507)**	9,697 (12,897)	7,222 (9,605)	10,932 (14,540)
The bolded amounts highlight the lowest and highest reimbursement					

cystoscopy. Overall, the study found that the savings per patient was €1195 (for a cost of 5-ALA of €135). Similarly, in a German Hospital, Sievert et al. (2009)[36] performed a TURBT cost calculation comparing conventional TURBT with PDD TURBT based on a diagnostically related group. Additional costs, such as the equipment required, were included in the calculation. They concluded that due to improved diagnosis, less TURS were required, resulting in a saving of approximately €140 per patient per year. In Sweden[39] in a population of 2,032 newly diagnosed patients, 23 cystectomies were prevented; 180 fewer TURBTs were required, resulting in savings of 1.3 million SEK (1.9%). An unpublished study in Holland in 2009 used a mathematical model based on the number of incidences of NMIBC in 2005, the 2008 EAU guidelines for NMIBC therapy, the EORTC questionnaire for recurrence rates ± BL with HAL, and discussion with Dutch experts. The 1 year estimation included costs for all new and recurrent NMIBC incorporating therapy. The study found a cost reduction of 2.5% when BL cystoscopy was used, (from 43.9 m€ to 42.7 m€). These savings were even higher when recurrent low risk and intermediate risk were not included: 6.7% (2.9m€).

HAL is well tolerated therefore toxicity is not a major consideration. Longer follow up will result in cumulative cost savings; however quality of life (QoL) improvement has not been included in the studies described. In Italy (2013) a report was submitted to the Italian Medicine Agency for Drugs (AIFA). The report aims to have HAL fully reimbursed at a national level. The report used very conservative assumptions and was developed within the health technology assessment programme of the National Institute for Health Research (NIHR). All TURBTs (new and recurrent patients) were considered and expert input was used. The report concluded that HAL is cost effective and improves QoL.

In conclusion, the power of BL cystoscopy should not be underestimated. Although there is some initial investment required, it has been shown to be cost effective in tested health systems and well tolerated by the patient.

New Developments in Instillation Therapy

Savino Di Stasi

The main role of intravesical chemotherapy in non-muscle invasive bladder cancer (NMIBC) is immediately after a TURBT; however the use of intravesical chemotherapy is suboptimal for patients with multiple tumours.

Studies on cultured human bladder tumours have indicated that the Mitomycin C (MMC) concentrations required to produce 90% inhibition of tumour cell proliferation are: urothelium 16 µg/ml, Lamina Propria 25 µg/ml, and muscularis 43 µg/ml.[40] Extensive investigation of passive diffusion studies in bladder wall of dogs and in patients undergoing radical cystectomy indicate that concentrations required to produce a cytotoxic effect are reached in 100% of cases for the urothelium, 20% in the lamina propria and 17% in the muscularis.[41-42]

There are 2 approaches to enhance drug transport in the bladder wall. They are device assisted intravesical chemotherapy, specifically chemo-hyperthermia (Synergo®) and Electro Motive Drug Administration (EMDA®).

HYPERTHERMIA

Hyperthermia enhances the effect of chemotherapy on the inhibition of DNA synthesis, increases cell membrane permeability and drug uptake by the cancer cells. The most common form of hyperthermia uses the Synergo system. Synergo delivers controlled hyperthermia (42 to 44°C) to the superficial layers of the bladder wall through radio-frequency microwave energy via an antenna unit in the tip of a special catheter. A systematic review of 22 studies including 357 patients indicated that intravesical chemo-hyperthermia significantly reduces the risk in NMIBC recurrences and also appears to improve bladder preservation rate (87.5%) when compared with MMC alone . However, due to limited number of controlled trials and different study designs, definitive conclusions cannot be drawn with respect to time to recurrences and time to progression.[43]

A marker lesion study demonstrated a significantly higher complete response rate after chemo-hyperthermia compared with mitomycin alone (66% versus 22%), although time to recurrence was similar.[44] In a prospective, multicentre randomised

trial, with an overall follow-up of 24 months, the recurrence rate after MMC alone (57.5%) was several-fold higher than of chemo-hyperthermia (17.1%).[45] After a median follow-up of 91 months recurrences were noted in 40% of chemo-hyperthermia patients and 80% of patients treated with MMC alone; the disease-free survival rate for chemo-hyperthermia and MMC alone were 53% and 15%, respectively.[46]

A study of intravesical hyperthermia and MMC for primary or BCG-failing carcinoma in situ (CIS) of the bladder showed a 92% complete response rate after 12 months, and 51% after 27 months.[47] A further study[48] showed that intravesical chemo-hyperthermia can be an effective adjuvant therapy in patients with T1-G3 bladder cancer. After a median follow-up of 18 months the recurrence and progression rates were 33.3%, and 7.8%, respectively. In addition, combined thermo-chemotherapy for recurrent bladder cancer after BCG treatment has been shown to be effective with a 2 year overall disease-free survival rate of 56%.and a progression rate of 6.6%. The outcome of this study shows that chemo-hyperthermia may be useful for patients with NMIBC who recur after BCG treatment.[49]

The most common adverse effects reported following chemo-hyperthermia were posterior thermal bladder wall reaction, pelvic pain, dysuria, bladder spasms, cutaneous rash, haematuria, and reduced bladder capacity.[43] Most studies reported that these symptoms were mild. Posterior bladder wall thermal reaction was commonly seen in instances where the heating device was in contact with the bladder wall during therapy; this is not usually associated with symptoms and disappears spontaneously after several months.

EDMA

EDMA is described as accelerated drug transport under the influence of an electric field. MMC is non-ionized within the tolerable physiological range and its electromotive mode of delivery is by electroosmosis.[50] Laboratory studies demonstrated that compared with passive diffusion (PD), EMDA significantly enhances MMC transport and decreases variability of delivery in all the layers of the bladder wall, with IC90 levels achieved in all cases in the urothelium and lamina propria.[51]

A randomised study comparing EMDA/MMC versus PD/MMC versus BCG in 108 patients with multifocal CIS of the bladder showed that intravesical EMDA increases bladder uptake of MMC, resulting in an improved response rate in cases of high risk NMIBC.[52] The complete response for EMDA/MCC versus PD/MMC at 3 and 6 months was 53% versus 28% (p=0.0361) and 58% versus 31% (p=0.0123) respectively. For BCG, the responses were 56% (p=0.0361) and 64% (p=0.0123). The median time to recurrence was 15 months for EMDA/MMC versus 9.1 months for PD/MMC, and for BCG it was 17.8 months (p=0.013). Peak plasma MMC was significantly higher following EMDA/MMC than after PD/MMC (43 ng/ml versus 8 ng/ml), indicating MMC bladder content absorption. Side effects were significantly more prominent in the BCG arm, and there were no statistical differences between the two MMC arms. The long-term results of this study (median follow-82.5 months) suggested that, in terms of complete response and disease-free interval, intravesical EMDA/MMC and BCG were effective treatments for CIS of the bladder. Both seemed more efficacious than passive MMC transport. As the response rates overlapped, EMDA/MMC may be an alternative or rather a complementary therapy, to BCG.

In a randomised study the combination of

Table 4: EMDA/MMC vs PD/MMC vs BCG. Di Stasi SM et al. J Urol 2003

Carcinoma in situ				
Median follow-up 82.5 months				
	PD/MMC (n=36)	EMDA/MMC (n=36)	BCG (n=36)	p-value
Complete Response Rates				
– 6 months	27.8	52.8	55.5	0.0361
– 3 months	30.5	58.3	63.9	0.0123
Crossover	----	23.1	35.0	0.5114
Recurrence				
– % Patients	82.8	66.7	65.7	0.2211
– Median time to rec. mos	9.1	15.0	17.8	<0.0001
Disease progression				
– % Patients	44.4	30.6	27.8	0.0612
– Median time to pro. mos	21.5	26.9	27.3	
Mortality Rates				
– Any cause	52.8	47.2	52.8	0.4964
– Bladder cancer	30.6	22.2	22.2	0.4941

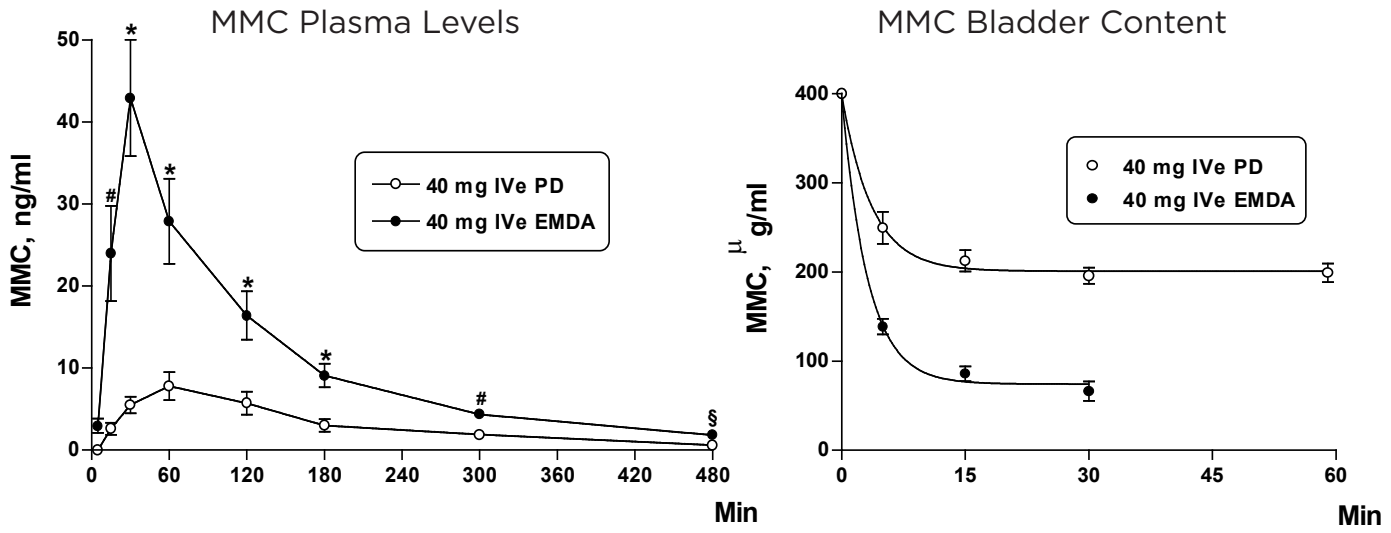


Figure 4: MMC Pharmacokinetics

intravesical BCG and EMDA/MMC was compared with BCG alone in 212 patients with stage pT1 urothelial bladder cancer.[53] The median follow-up was 88 months. The results of the study showed that the patients assigned to the sequential BCG and EDMA/MMC arm had a significantly higher disease-free interval, lower rates of recurrence, disease progression overall mortality and reduced disease specific mortality compared with patients assigned to BCG alone. (Table 5)

The 2 groups did not differ in the frequency or the severity of side-effects, these were mainly localised to the bladder. The timing schedule and delivery techniques used in this trial were selected to keep the benefits of both drugs at an optimum. It is possible that the efficacy of the BCG and EMDA/MMC combination is due to BCG-induced inflammation which potentially increases the permeability of the bladder mucosa so that MMC can reach the target tissue more easily and exert its anticancer effect.

Table 5: Sequential BCG and EMDA/MMC compared with BCG alone

Sequential BCG and EMDA/MMC vs. BCG alone Median follow-up 88 months				
	BCG and EMDA/ MMC	BCG	Difference	P-value
Disease-free interval (months)	69	21	48	0.0012
Recurrence (%)	41.9	57.9	16	0.0012
Progression (%)	9.3	21.9	12.6	0.0040
Overall mortality (%)	21.5	32.4	10.9	0.0450
Disease specific mortality (%)	5.6	16.2	10.6	0.0100

European reports indicate that administering one single dose of intravesical chemotherapy a few hours after TURBT, targeted to destroy floating tumour cells that could implant at the resection site, significantly reduces the recurrence rate. Although, recommended, this approach seems to be inadequate for patients with multiple tumours. An early single intravesical EMDA/MMC instillation after TURBT is not recommended because the catheterisation may cause bladder spasm, and furthermore, haematuria and bladder perforation are absolute contraindications to intravesical EMDA /MMC.

A randomised, controlled trial evaluated the effects of immediate pre-TURBT single intravesical EMDA/MMC instillation versus immediate post-TURBT single intravesical PD/MMC instillation versus TURBT alone in 363 patients with primary NMIBC.[54] After a median follow-up of 85 months, the number of patients with recurrence was significantly higher (64%) in the TURBT alone arm and in the immediate single PD/MMC post-TURBT instillation arm (59%), compared with the immediate single EMDA/MMC pre-TURBT instillation arm (38%, p=<0.001). The general trend of fewer recurrences was apparent in all major categories in the group that received intravesical EMDA/MMC instillation before the TURBT and particularly in patients with multifocal disease. The median disease free interval was 13 months in the TURBT alone arm, 16 months in the immediate single PD/MMC post-TURBT instillation arm, and significantly higher (57

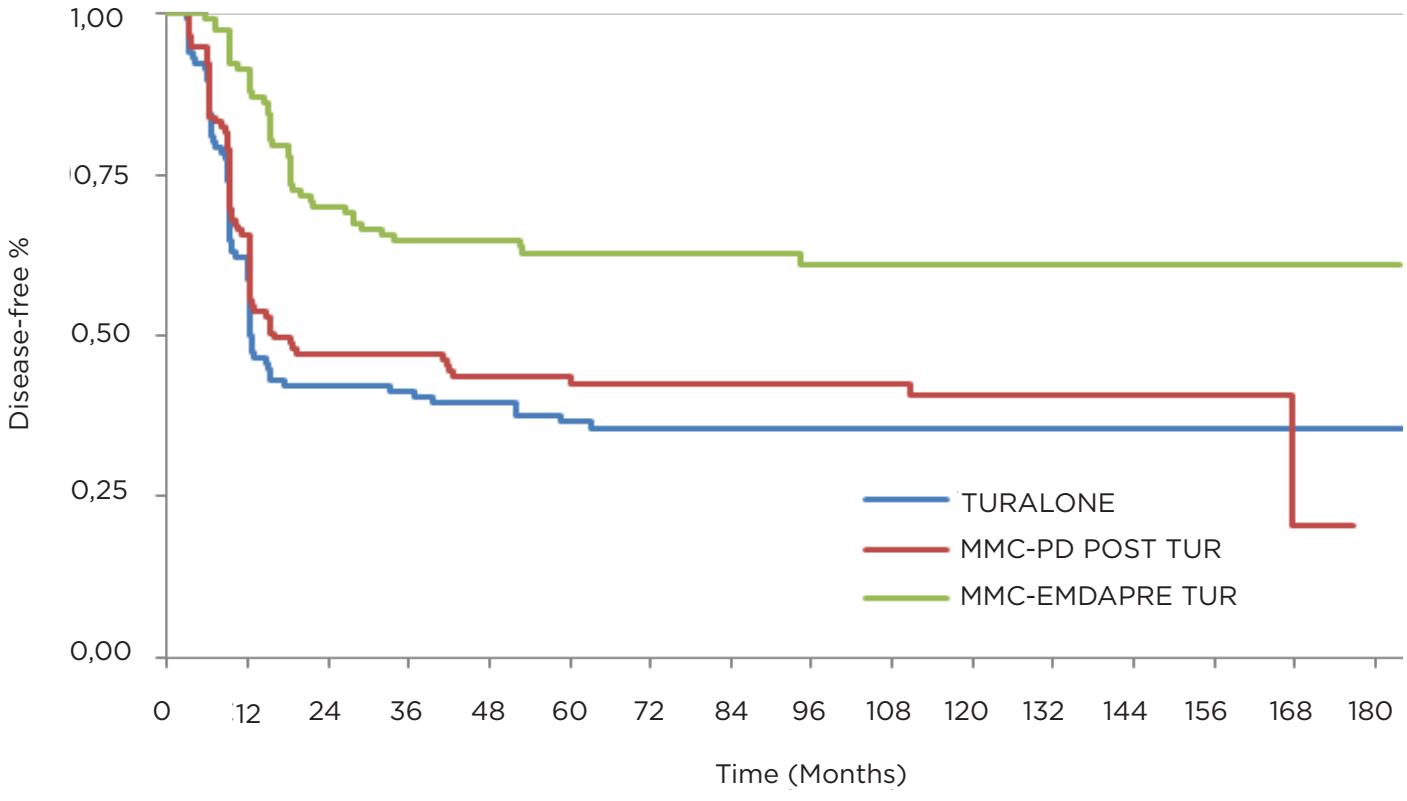
months) in the immediate single EMDA/MMC pre-TURBT instillation arm (p=<0.001). Overall disease free interval shown by the Kaplan Meier analysis showed immediate pre-TURBT single EMDA/MMC instillation provided an overall significant benefit over immediate post-TURBT single PD/MMC instillation or TURBT alone.

In total, 99% of the EMDA/MMC pre-TURBT group completed the treatment. In the PD/MMC post-TURBT group, treatment was not administered in 21% of patients due to overt bladder perforation (8%) or macroscopic haematuria (13%), and treatment was stopped after 10 to 15 minutes in 24% of patients due to discomfort/pain, bladder spasms, or leakage of drug solution. Persistent lower urinary-tract symptoms reports were more frequent in the PD/MMC post-TURBT group compared to the EMDA/MMC pre-TURBT or the TURBT alone group.

Colombo et al. (2001)[55] compared chemo-hyperthermia against EMDA/MMC and PD/MMC in a retrospective pilot study on marker lesions. The complete response rate was 28% in the PD/MMC arm, 40% in the EMDA/MMC arm, and 66% in the chemo-hyperthermia arm. Local toxicity was more severe after chemo-hyperthermia than after PD/MMC or EMDA/MMC. However, there were weaknesses in the design of this study that should be considered in conjunction with the results; the patients were free to choose their treatment, and duration of therapy and MMC concentration were different among the 3 arms. In addition, patients were not followed for long-term risk of recurrence or progression.

In conclusion, intravesical device assisted MMC chemotherapy administration is well tolerated, feasible, and more effective than MMC alone. Intravesical EMDA/MMC is well tolerated and less expensive than chemo-hyperthermia with the Synergo system. New frameworks for treatment of NMIBC, for example, sequential intravesical BCG and EMDA/MMC, as well as intravesical EMDA/MMC immediately before TURBT have provided promising feasible, and more effective than MMC alone. Intravesical EMDA/MMC is well tolerated and less expensive than chemo-hyperthermia with the Synergo system. New frameworks for treatment of NMIBC, for example, sequential intravesical BCG and EMDA/MMC, as well as intravesical EMDA/MMC immediately before TURBT have provided promising results with higher remission rates and longer remission times, indicating that these

Figure 5: Overall Disease-Free Interval



therapeutic strategies should be used as a priority to minimise the costs of disease management. When managing NMIBC, the role of intravesical device assisted chemotherapy needs to be assessed in depth and the advantages not ignored. It would be beneficial if future developments enable intravesical device assisted chemotherapy to be added to standardised treatment protocols.

Conclusions

Maurizio Brausi

It is evident that adequate first TURBT is essential and that the TUR is of a high standard. HAL can improve results by decreasing recurrence rates and increasing the detection rate of CIS. International data and good meta-analyses support the use of BL cystoscopy, emphasising that BL cystoscopy is optimal in high risk patients with high risk tumours. In addition, in tested health care systems BL TURBT has been shown to be cost effective. Hyperthermia (Synergo®) and EMDA with MMC are effective in intermediate and high risk patients. However, side effects and costs are lower with EMDA. A single instillation of MMC with EMDA prior to TUR is effective, indicating that this new approach will be of increasing benefit to patients with multiple tumours.

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MULTIPLEX URINARY TESTS FOR BLADDER CANCER DIAGNOSIS

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ABSTRACT

The development of accurate and reliable molecular assays that could diagnose bladder cancer would be of significant benefit to both patients and the healthcare system. Non-invasive assays that have utility not only for diagnosis, but also for monitoring disease recurrence and response to treatment, are needed. Current urinary tests lack sufficient sensitivity or specificity, often because of a reliance on single biomarkers, but high-throughput technologies are enabling the derivation of more accurate panels of biomarkers. In this article, we review some of the promising investigational studies that are revealing multiplex biomarker signatures that may augment current bladder cancer detection strategies.

Keywords: bladder cancer, biomarkers, non-invasive, urinalysis, diagnosis.

INTRODUCTION

Bladder cancer (BCa) is one of the most prevalent cancers worldwide and there are over 70,000 new cases of BCa each year in the United States alone.[1] If detected early, the five-year survival rate for BCa is >90%, thus timely intervention can dramatically increase the probability of patient survival. Radical surgery is required for muscle invasive lesions, but more prevalent non-muscle invasive BCas can be treated through transurethral resection of the tumour. Unfortunately, more than 70% of patients with non-muscle invasive BCa will have disease recurrence within two years of treatment. Thus, extensive long-term surveillance and repeated surgical intervention are needed to prevent progression of early-stage tumours to the more lethal invasive disease.

The gold standard for BCa diagnosis remains cystoscopic examination of the bladder coupled with voided urine cytology (VUC), the cytologic examination of cellular material present in the urine.[2-4] Cystoscopy is an uncomfortable and costly invasive procedure, which may require anesthetisation of the patient. Evaluation by VUC relies on the microscopic visualisation of shed cancer cells in voided urine. The technique performs well with high-grade and high-stage tumours (T2-T4), but the sensitivity for detecting low-stage tumours is low, ranging from only 20% to 40%.[4-6] The development of accurate and reliable urinary assays that can reduce the need for cystoscopy would be of tremendous benefit to both patients and the healthcare system.

A number of commercial molecular tests have been FDA-approved for specific scenarios. These tests include the measurement of soluble proteins such as: bladder tumour antigen (BTA), nuclear matrix protein 22 (NMP22), proteins detected on fixed urothelial cells (ImmunoCyt™), and chromosomal aberrations detected by fluorescent in situ hybridisation (UroVysion™). Unfortunately, to date, none of these tests have achieved combined sensitivity and specificity values to replace the established cystoscopy and VUC clinical evaluations. This may be due to the reliance of these tests on monitoring single biomarkers. No one biomarker is going to achieve accuracy across the breadth of clinical presentation seen at the urology clinic as not all BCas will harbour any single molecular change.[7] This is supported by the finding that when these tests are combined in one cohort, improvement over single tests is observed,[8-10] however, proprietary issues mean that such combinations are not currently feasible. What is needed are multiplex biomarker assays that can be developed into risk scores and nomograms such that an assay can be applicable over a broad range of disease states. Below, we describe some of the advances in multiplex biomarker discovery for the potential non-invasive diagnosis and monitoring of BCa. In this short review, we focus on

protein and RNA-based studies. Numerous studies that describe alterations in DNA sequence, DNA methylation, and metabolomic signatures associated with BCa have been described elsewhere.[11]

BIOMARKER SIGNATURES FOR NON-INVASIVE BCa DETECTION

Protein Biomarkers

The appropriate use of advanced proteomics technologies has the potential to provide highly efficient biomarkers for BCa detection and monitoring. Capillary electrophoresis-mass spectrometry (CE-MS) was used by Theodorescu et al.[12] to identify urinary biomarkers for BCa in a training set composed of 46 patients with urothelial carcinoma and 33 healthy volunteers. These biomarkers were further refined using CE-MS spectra of another cohort of urine samples from healthy volunteers and patients with malignant and non-malignant genitourinary diseases. A diagnostic biomarker signature of 22 urinary peptides was established using this two-step approach. In a validation study, this signature enabled the correct classification of all urothelial carcinoma patients in a test set containing 31 urothelial carcinoma patients and 138 non-malignant genitourinary disease patients.[12] Another study used an iTRAQ (isobaric tag for relative and absolute quantitation) technique to discover proteins that were differentially expressed between pooled urine samples and non-tumour controls. This strategy identified 55 candidate biomarker proteins.

Conventional techniques confirmed that the level of apolipoprotein A-I (APOA1) was significantly elevated in urine samples from BCa patients.[13] In our own studies, we used a glycoprotein enrichment strategy to profile urine samples from 100 subjects.[14] Combining specific glycoproteins with targets identified in our genomic studies (described below) we subsequently investigated the accuracy of various combinations of protein biomarkers for diagnostic urinalysis in a series of ELISA studies.[15-17] Multivariate analysis identified an 8-protein biomarker panel that achieved 92% sensitivity and 97% specificity in an independent cohort of 64 patients with BCa and 63 controls.[18] The performance of these biomarker panels was far better than current urinalysis tests in the same cohort. Validation of these multiplex biomarker panels in larger, more diverse cohorts is underway. The studies described above show the power of MS-based urinary analysis for the discovery of potential biomarkers. Continuing proteomic technological developments, such as assays for phosphoproteins, glycoproteins or phospho-lipoproteins can achieve reduction of sample complexity for further proteomic analysis of biological fluids, so additional panels of proteins that can be developed into accurate and simple urinalysis assays are likely to be derived in the future.

RNA Markers

Given the advances in RNA/DNA sequencing and hybridisation platforms, one of the most promising sources for the derivation of multiplex diagnostic biomarker signatures is the tumour cell transcriptome. The majority of BCa gene expression profiling studies focused on the analysis of excised solid tumour tissue. These studies have identified gene signatures that are associated with tumour stage,[19-20] disease recurrence and outcome prediction,[19-21] and are most applicable to the development of assays that will aid the histological evaluation of biopsy or excised tumour material. Normal tissue is not readily available for comparison for obvious reasons. Conversely, the analysis of gene expression in naturally shed urothelia (present in all voided urine samples) has several advantages, not least of which is the availability of samples from a range of disease conditions as well as healthy controls. Through polymerase chain reaction (PCR) amplification the analysis can be performed on the minimal cellular material obtained from naturally voided urine, and the detection methods are accurate, quantitative, and economical.

Holyoake et al.[22] used molecular profiling of solid tissues to identify genes over-expressed in tumour stages Ta, T1 or >T1, relative to non-tumour epithelial tissues and inflammatory cells. Using this strategy, transcripts of four genes CDC2, MDK, IGFBP5, and HOXA13 were selected for development of a quantitative RT-PCR urine assay for BCa detection and disease risk stratification of patients. The measurement of the combination of mRNA markers detected BCa at a sensitivity of 85% and a specificity of 80% across all stages, with the best performance with stages >T1 and tumours >1cm in diameter.[22] A recent study by the same investigators compared the performance of assays derived from this biomarker panel in a cohort of 485 patients. The test achieved higher sensitivity (62%) than NMP22 and cytology at a pre-specified 85% specificity, and a modification of the assay detected 82% of BCa cases.[23] Hanke et al.[24] analysed the expression of a selected panel of mRNAs as biomarkers of BCa in whole urine, cell pellets and clarified urine. In a cohort of 98 subjects, they found that the ratio of v-ets erythroblastosis virus E26 oncogene homolog 2 (ETS2) to urokinase plasminogen activator (PLAU) in whole urine facilitated the detection of BCa with a sensitivity of 75% at 100% specificity. Other mRNA-based diagnostic urinalyses have targeted BIRC5 (survivin), HYAL1, KRT20 and MUC7.[25-27] These targets performed similarly at sensitivities between 62-90%, and confirmed that combinations of two to three mRNA markers perform

In our own studies we performed genome-wide mRNA profiles of urothelia obtained from over 90 urine samples. We reasoned that profiling the actual material that would be subject to diagnostic assay in the clinic would circumvent any confounding factors inherent to tissue profiling. The resulting profiles were analysed using advanced feature selection algorithms[28-30] to reveal an optimal gene signature for BCa association. A 14-gene signature model was derived and monitoring of this signature using quantitative RT-PCR was able to detect BCa with 100% specificity at 90% sensitivity in an independent cohort of 81 cases.[31,32] In comparison, cytological evaluation of this cohort diagnosed only 35% of tumour cases correctly. In a study utilising a similar strategy, a panel of 384 genes identified in tissue-based analyses were subsequently tested in urothelial samples using quantitative RT-PCR.[33] These analyses identified a 12-gene signature that achieved high accuracy (89% sensitivity and 95% specificity) in identifying BCa cases in a cohort of 211 subjects. Despite significant differences between the studies, with respect to the biomarker discovery phase, both groups were able to derive molecular signatures that could accurately classify BCa samples. This demonstrates that a multiplex quantitative RT-PCR test on voided urine sample holds promise as a non-invasive urine-based assay in the evaluation of patients being investigated for BCa. Although a quantitative RT-PCR test has some upfront processing requirements, it has the advantage of being developed into an assay that can be automated and highly standardised for consistency between laboratory sites.

Another urothelial RNA source for potential biomarker discovery is the transcribed, non-protein coding microRNA (miRNAs) component. To date, over 1500 human miRNAs have been identified and characterised to some extent. Each miRNA controls the expression of multiple genes, and so this molecular family may represent an opportunity to identify biomarkers of a higher order. Assay-based profiling and deep-sequencing approaches for miRNA analysis are becoming routine, and studies targeting miRNAs as potential diagnostic biomarkers are increasing accordingly. Tumour tissue profiling studies have identified the expression of single miRNA transcripts as being associated with primary BCa or outcome, and some of the candidate biomarkers have been confirmed in urine samples.[34-39] More recent studies have derived signatures or panels of miRNA biomarkers with good diagnostic performance for urinalysis. Hanke et al.[40] examined the expression of 157 miRNAs in exfoliated urothelial cells using quantitative RT-PCR and reported that the ratio of miR-126 to miR-182 achieved 72% sensitivity and 82% specificity in a cohort of 47 samples. A quantitative PCR study of a panel of 15 miRNAs in 121 urine samples revealed that the combination of 3 miRNAs (135b/15b/1224-3p) detected BCa with high sensitivity (94.1%), but specificity was lower (51%).[41] The monitoring of miR-222 and miR-452 has been reported to be to helpful in tumour stratification and for non-invasive diagnosis,[38] and the expression of miR-96 and miR-183 have been shown to augment cytology and to correlate with advancing tumour grade and stage.[39]

CONCLUSION

The inadequate power of single biomarker assays means that the non-invasive detection of BCa remains a challenge. Advances in molecular techniques, especially profiling approaches, have enabled investigators to derive a new generation of compound molecular diagnostic signatures that may provide assays with the desired clinical utility. Such multiplex biomarker systems for BCa diagnosis are still at an early stage compared with the FDA-approved markers. Promising signatures and panels of markers have been derived and tested on varied cohorts, but require further validation in independent studies. The hope is they will provide informative robust tests across the broad range of clinical presentation. Once optimised, multiplex diagnostic assays may enter the clinical setting to augment, or eventually even replace, cystoscopy and/or cytology for diagnosis, disease recurrence monitoring, and the monitoring of response to treatment. A major advantage of multiple biomarker assays is the results can be input into algorithms to provide a continuous score for prediction of disease status or prognosis. Furthermore, algorithms that incorporate clinical data and molecular risk scores into a nomogram can give physicians the most valuable guidance regarding patient management.[42,43]

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PRACTICE PATTERNS FOR IMPROVING OUTCOMES IN WOMEN WITH ILEAL NEOBLADDER: AN EVIDENCE-BASED ANALYSIS

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ABSTRACT

Introduction: The aim of this review is to provide practice pattern on how to obtain best possible oncological and functional outcomes in women with orthotopic neobladder substitutes.

Evidence Synthesis: The treating surgeon has to balance oncological and functional risks as well as patient´s preferences and the final decision must be based on consent between the surgeon and the patient. Long-term survival can be achieved in the majority of neobladder patients even with extravesical, node-negative disease. Therefore, surgeons should not be reluctant to proceed with an ileal neobladder in patients with locally advanded tumour stage excluding T4b stage, any positive soft tissue surgical margin and bulky lymph node disease. During preoperative work-up, women with a positive bladder neck biopsy may be still candidates for an orthotopic neobladder unless a carefully obtained full-thickness biopsy of the urethra reveals evidence of malignancy. The key issue in the follow-up of women with neobladder is to achieve a neobladder capacity of 400-500mL, residual free voiding of sterile urine and the elimination of any outlet or upper tract obstruction. Medical conditions (i.e. arterial hypertension, diabetes mellitus) can also cause renal deterioration in the long-term and therefore demand early and thorough treatment.

Conclusions: The clinical background of the treating urologist is of paramount importance for appropriate patient selection, accurate surgical performance and adequate monitoring of women with ileal neobladders. A high level of patient compliance and willingness to undergo follow-up examinations at regular intervals is mandatory for improved outcomes.

Keywords: bladder cancer, follow-up, neobladder, radical cystectomy.

INTRODUCTION

Over the past two decades, large unicentre data have proven oncological and functional safety of using ileal neobladders in women.[1] While in the first postoperative years after radical surgery the patient's first priority is to survive the potentially recurring disease, functional aspects come to the patient's fore in the long-term.[2] Up to the early 1990s, many surgeons were reluctant to use ileal neobladder reconstruction in females because of the fear that the reduced urethral length might severely impair postoperative continence.[3] Yet, the neobladder procedure in women is challenging as surgical inaccuracy may lead to a broad range of complications with which the patient and referring urologist will have to struggle with in the long-term.[4] As hospital and surgeon volume has been increasingly recognised as critical determinants for reduced postoperative complication rate after neobladder reconstruction, centralisation of this challenging surgical procedure in high-volume centres has been increasingly advocated.[5] The aim of this review is to provide evidence-based practice pattern for obtaining the best possible functional and oncological outcomes in women with neobladder substitutes.

EVIDENCE SYNTHESIS

The Preoperative Decision-Making for Ileal Neobladder in Women

In clinical decision-making the optimal selection and preparation of a patient scheduled for neobladder reconstruction is of paramount importance. The treating surgeon has to balance oncological and functional risks as well as the patient's preferences. The final decision must be based on consent between the surgeon and the patient.[6] The treating surgeon has to pay particular attention to

various factors that may impair outcomes. A good renal function is a prerequisite for neobladder reconstruction as an increased postoperative reabsorption of acid urinary constituents through the ileal mucosa results in an increased acid load in neobladder patients compared to patients with ileal conduits.[7] Therefore, a woman with good renal function will easily compensate metabolic acidosis, provided the neobladder is emptied completely at regular intervals. Most surgeons consider women with creatinine clearance below 50ml/min to be ineligible for a neobladder.[8] Of note, in women with renal insufficiency owing to tumour-related hydronephrosis, upper tract desobstruction via nephrostomy allows for better preoperative evaluation of the exact renal function. In borderline cases, 51 Cr-EDTA clearance is more accurate than the estimated glomerular filtration rate to determine the exact renal function.[9] Furthermore, in younger women with borderline renal function it has to be taken into consideration that a natural age-dependent decline of renal function of approximately 1mL/min each year occurs over the age of 50.[10] Women after renal transplantation can safely undergo a neobladder procedure, provided the transplant and liver function are unrestricted.[11] Impaired liver function is critical in neobladder patients as it may not only lead to severe macrohematuria[12] but also to an aggravation of the renal function.[13] In women with complex or recurrent urethral strictures surgeons should be reserved in offering a neobladder approach as retention is likely to occur postoperatively.[14] Certainly, patients with any mental and physical impairments which preclude the ability to perform clean intermittent catheterisation in case of urinary retention are not candidates for an orthotopic neobladder. In terms of prior pelvic radiotherapy (due to gynecological malignancy) the exact radiotherapeutic field and applied dosage needs to be critically reappraised before excluding a women from an orthotopic approach a priori.[15-17*]

Intraoperative Management of the Urethra

Addressing oncological risk factors for tumour recurrence involving the neobladder in women is of utmost importance as tumour invasion into the neobladder has a detrimental impact on patient´s quality of life and survival.[18] Tumour location at the bladder neck, multiplicity and presence of carcinoma in situ have been reported to be risk factors both for a positive urethral margin and urethral recurrence.[16,18] Therefore, some surgeons advocate that bladder neck biopsy in women is sufficient enough to exclude a malignant urethral margin at cystectomy.[19] Others rely completely on the results of intraoperative frozen section analysis of the urethral margin.[20] However, recurrences involving the neobladder have been reported despite the use of frozen section at the time of surgery.[21-22] These data underlie that the low sensitivity may be not attributable to a low predictive accuracy of frozen section analysis, but rather to undersampling which strengthens the importance of performing a full-thickness biopsy of the urethra. However, as the distal urethral margin may be tumour-free despite the presence of a bladder neck tumour (in the study by Stein et al. in ~60% of the cases[23]), exclusion of women from an orthotopic approach due to primary tumour location at the bladder neck is not justified unless a carefully obtained frozen section of the distal urethral margin evidences malignancy. In conclusion, to reduce the risk of urethral recurrence surgeons need to carefully check the bladder neck at transurethral resection and focus on enlarged pelvic or inguinal lymph nodes at staging investigations. The use of frozen section analysis of the distal urethal margin in case of bladder neck tumour involvement may still allow for the performance of an orthotopic diversion in women, without putting them into an increased risk for urethral recurrence.

Neobladder Reconstruction in Advanced Tumour Stages - To Do or Not To Do?

In terms of tumour stage, the largest neobladder series in women have reported similar 10-year recurrence-free survival rates in organ-confined (≤pT2N0) and extravesical node-negative (≥pT3aN0) disease ranging between 67-71%.[22] These data were confirmed in other series reporting 5-year overall survival rates between node-negative patients with ≤pT2N0 and ≥pT3N0 of 80% and 82%, respectively.[24] Therefore, surgeons should not be reluctant to proceed with an ileal neobladder in patients with locally advanced tumour stage or limited lymph node tumour burden if the affected lymph nodes are completely removable. However, in patients with bulky lymph nodes (>5cm), pelvic or abdominal wall infiltration (staged cT4b) or positive soft tissue surgical margin the treating surgeon should refrain from any orthotopic approach since postoperative adhesions to the pelvic wall will inevitably result in tumour invasion of the neobladder.[18]

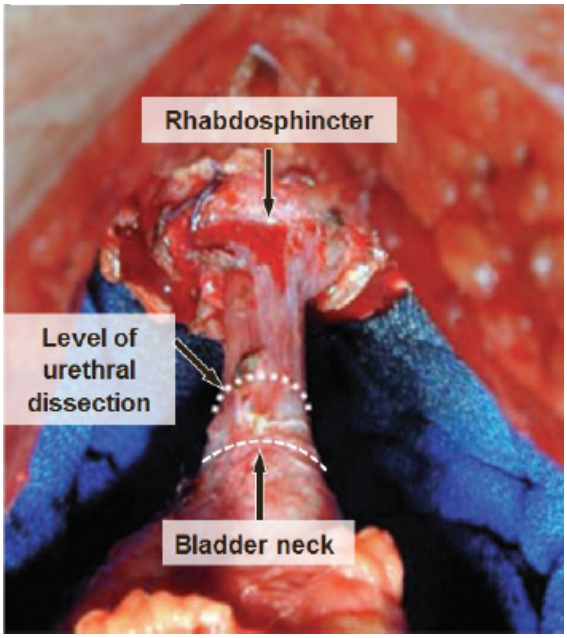
Surgical Aspects for the Reconstruction of the Neobladder Reservoir

It is well-known that postoperative upper tract obstruction due to ureterointestinal stenosis is one leading causes of renal deterioration after neobladder reconstruction. Nonetheless, the majority of studies have shown that neither the use of refluxing nor antirefluxing ureteral implantation techniques provide superior results in terms of improved postoperative renal function.[7,25] Attempting nerve-sparing cystectomy has a positive

impact on postoperative urethral pressure profile[26] and results in improved continence rates.[27] Sparing the lateral vaginal walls allows for improved continence and sexual function via preservation of autonomic nerve supply to the urethra and vaginal lubrication.[27-28]

Another important aspect is the risk of urinary retention which has been shown to be significantly higher in women than in men.[7,24] Large-capacity reservoirs store urine at lower end-filling pressures but the use of less bowel for the creation of a spherical reservoir carries a lower risk for early absorptive complications.[29] Women with large-capacity reservoirs (derived from a 60-70cm ileal segment) will most probably gain earlier satisfactory postoperative continence than women with neobladders of less ileal length. However, long-term continence rates seem not to vary between both groups[24] as the functional capacity of orthotopic reservoir made of shorter ileal segment increases rapidly within the first weeks after surgery from around 150mL to 400-500mL. Conversely, the use of excessive length of ileum may produce a "floppy" low-pressure reservoir that is more prone to retention.[19] In this respect, patient compliance and willingness to actively exercise storing within and emptying the neobladder is of paramount importance in the first months after surgery. To prevent postoperative urinary retention in women, the urethra should be divided approximately 1cm below the bladder neck (Figure 1). Otherwise a mechanical kink at the level of urethro-intestinal anastomosis may occur, especially as orthotopic pouches tend to fall posteriorly during Valsalva maneuver which can be demonstrated on lateral straining cystogram.[30] In this respect, creating posterior support with a omental flap from the posterior vaginal wall to the edges of the endopelvic facia may have some preventive effects.[31]

Figure 1: Level of urethral dissection in relation to the bladder neck and rhabdosphincter in a woman undergoing radical cystectomy with orthotopic neobladder.



Critical Aspects During Follow-Up of Women with Neobladder

The risk of urethral recurrence after neobladder formation in women is quite low (less than 1%).[32] While symptomatic women presenting with urethral bleeding, pain, or palpable mass have to be evaluated promptly, there is no clear evidence supporting a survival benefit with use of a defined follow-up schedule.[32-34] It seems therefore reasonable to tailor surveillance regimens individually according to the patient´s risk factors for urethral recurrence. In the long-term, there are many potential reasons which may cause renal deterioration following orthotopic neobladder reconstruction. Basically, any condition which allows the transmission of high pressure or infected urine into the kidneys can cause renal deterioration (i.e. ureterointestinal stenosis, stone formation and increased post-void residual urine). During follow-up, key issues are to achieve a neobladder capacity of 400-500mL, residual free voiding of sterile urine, and the elimination of any outlet or upper tract obstruction. Recurrent urinary tract infections (even if not symptomatic) should prompt physicians to exclude the presence of residual urine volume and check for electrolyte imbalances. Neobladder patients are at risk of salt loss as sodium excretion is increased through the ileal mucosa,[35] which can cause various symptoms (i.e. apathy, nausea, vomiting, anorexia). These electrolyte imbalances can easily be corrected by sodium bicarbonate supplementation and sodium-rich food intake. Untreated chronic metabolic acidosis also has adverse effects on bone mineral density and may lead to an increased risk for skeletal-related events.[36] Furthermore, vitamin B12 supplementation may become necessary in the long-term, especially in large-capacity reservoirs, and should be checked from the third postoperative year onwards.[7**]

The treating urologists need to be aware of the fact that a postoperative decline in renal function may also be attributable to poorly regulated metabolic diseases (i.e. diabetes, arterial hypertension) or drug-related side effects. Therefore, patients' medication list needs to be checked regularly, and any medical conditions which may cause renal deterioration in the long-term needs to be treated as thoroughly as possible.

CONCLUSION

The clinical background of the treating urologist is of paramount importance for appropriate patient selection, accurate surgical performance and adequate monitoring of neobladder patients. Improved outcomes in women with ileal neobladder mandate a high level of patient compliance and willingness to undergo examinations at regular intervals.

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PROSTATIC INFLAMMATION IS DETERMINANT FOR PROSTATE OVERGROWTH AND LUTS SEVERITY IN MEN WITH METABOLIC SYNDROME: HIGHLIGHTS FROM TWO RECENTLY PUBLISHED MULTICENTRE STUDIES

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ABSTRACT

Introduction: Several evidences have pointed out the possible association between Metabolic Syndrome (MetS) and low urinary tract symptoms (LUTS)/benign prostate hyperplasia (BPH). Recent epidemiological and histopatological evidences suggested chronic inflammation is a crucial event in BPH pathogenesis. Aim of this study is to demonstrate the correlation among pre-operatory LUTS/BPH severity, MetS features and inflammatory infiltrates in prostatectomy specimens of patients with BPH, highlighting the results of two recently published multicentre studies analyzing all the data from a preclinical and clinical point of view.

Materials and methods: We conducted two retrospective study in 271 and 244 consecutive men treated with simple prostatectomy for LUTS/BPH in two tertiary referral centres. Prostate diameters and volume were measured by transrectal ultrasound, LUTS were scored by IPSS, and obstruction diagnosed by uroflowmetry. MetS was defined according to DF & AHA/NHLBI criteria. The inflammatory infiltrate was investigated according to the scoring system of chronic prostatitis (CP-CPPS) and scored as inflammation score (IS) ranging 3 to 9 and glandular disruption (GD). In addition, we investigated the in vitro inflammatory effects of metabolic insults on human prostatic myofibroblast cells isolated from BPH patients (hBPH).

Results: Of 271 men, 86 (31.7%) were affected by MetS. Prostatic volume and the anterior-posterior (AP) diameter were positively associated to the number of MetS components. Among MetS determinants, only dyslipidaemia (increased serum triglycerides and reduced serum HDL levels) was significantly associated with an increased risk of having a prostatic volume >60cm3. IS in prostatectomy specimens showed a step-wise association with number of MetS factors (p=0.001). Dyslipidaemia was the only factor significantly associated with IS. Positive significant correlations among MetS, IS, GD and IPSS Scores were observed. In myofibroblastic hBPH oxidized low-density lipoprotein (oxLDL) showed the highest secretion of IL-8 (>10-folds)-a surrogate marker of prostate inflammation-as well as IL-6, and bFGF.

Conclusions: MetS and dyslipidaemia are associated with prostate overgrowth and inflammation. In particular, with a selective increase of prostatic AP diameter, leading to a modification of prostatic shape. Hence, MetS can be regarded as a new determinant of prostate inflammation and BPH progression in men with severe LUTS.

Keywords: bladder cancer, follow-up, neobladder, radical cystectomy.

INTRODUCTION

Benign prostatic hyperplasia (BPH), considered as a chronic disease with early initiation, slow progression and high prevalence in the adult male, is frequently associated with lower urinary tract symptoms (LUTS) in elderly men.[1] Traditionally, male LUTS were thought to be merely caused by a benign prostatic enlargement (BPE). However, the lack of a complete correspondence between BPE and LUTS has meant a struggle to identify other causative relationships linking prostatic overgrowth, bladder outlet obstruction and LUTS.[2]

Emerging data indicate that a spectrum of age-related disorders, such as metabolic syndrome (MetS), type 2 diabetes (T2DM), cardiovascular (CV) disease, hypogonadism or a combination thereof, have a heretofore unrecognised negative impact on LUTS. Several MetS components have been closely associated with BPH, suggesting that MetS has very heterogeneous clinical ramification.[3-5]

The faster development and progression of symptomatic BPH[3] and a consequent major request of BPH surgery[6] in men with metabolic alterations, supports the hypothesis that pathological alterations characterising MetS can also influence the prostatic overgrowth and the development of LUTS. Although the molecular and cellular mechanisms involved in stromal and epithelial prostate modification leading to BPH/LUTS remain unclear, chronic inflammation has been proposed as a candidate promoter mechanism, and MetS can broadly be considered a systemic inflammatory state and a chronic inflammation-driven tissue remodelling and overgrowth.[7] Preclinical studies in genomic and non-genomic animal models of different metabolic diseases have suggested a potential causative association between metabolic derangements and BPH development and progression.[8]

The aim of this paper is to examine the correlation among pre-operatory LUTS/BPH severity and MetS features, to evaluate whether MetS is associated with BPH-related inflammation and to investigate the in vitro inflammatory effects of different metabolic insults on human prostatic myofibroblast cells isolated from BPH patients (hBPH), reporting the results of two recently published preclinical and clinical multicentre studies.[9-10]

MATERIAL AND METHODS

Study Population and Design

Two consecutive cohorts of 271 patients treated with simple prostatectomy for BPH, were retrospectively selected. Height, weight, waist circumference (WC) and blood pressure, were measured and Body mass index (BMI) was calculated. Blood samples were drawn in the morning for determination of blood glucose, total cholesterol, HDL cholesterol and triglycerides.

Open transvesical prostatectomy (OP) or transurethral resection of prostate (TURP) were performed as previously reported.[11-12] Surgical specimens (taken by at least three different sites of the adenomatous tissue) were collected with sterile procedure, and used for both histological examination and inflammatory definition.

Assessment of LUTS, BPH Features, MetS and Characterisation of Prostatic Inflammatory Infiltrates

LUTS were measured by the International Prostate Symptom Score (IPSS) within one month from surgery. Meanwhile, prostate diameters (AP: antero-posterior; CC: cranio-caudal; LL: latero-lateral) were measured by TRUS and prostate volume was calculated using the ellipsoid formula ($AP \times CC \times LL \times \pi/6$), while maximum and average flow rate (Qmax, Qave) were obtained by uroflowmetry before surgery.

MetS was defined according to the criteria published by the International Diabetes Federation (IDF) & American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI)[13], and was based on single blood values (e.g. fasting glucose levels, lipid profiles).

All surgical specimens were examined on hematoxylin eosin-stained sections by two independent pathologists, blinded of clinical information. Samples were investigated for the presence of an inflammatory infiltrate, according to the classification of chronic prostatitis (CP-CPPS) of the National Institutes of Health.[14] The grading methods were based on an "inflammatory score" (IS). Moreover, the resulting destruction of the glandular epithelium due to the massive inflammatory infiltration was considered as a further marker of flogosis: "glandular disruption" (GD).[15] In addition, we investigated the in vitro inflammatory effects of metabolic insults on myofibroblastic hBPH, using three different primary human prostatic myofibroblast cultures obtained from three patients undergoing suprapubic adenomectomy for BPH (hBPH) as control hBPH cells, as previously described.[10]

RESULTS

Overall, 271 patients treated with simple prostatectomy for BPH were enrolled in the first study (clinical) and 244 in the second (preclinical), as 27 patients were excluded. Eighty-six men (31.7%) were affected by MetS. In particular, 46 (17.0%) presented with 3/5 parameters of

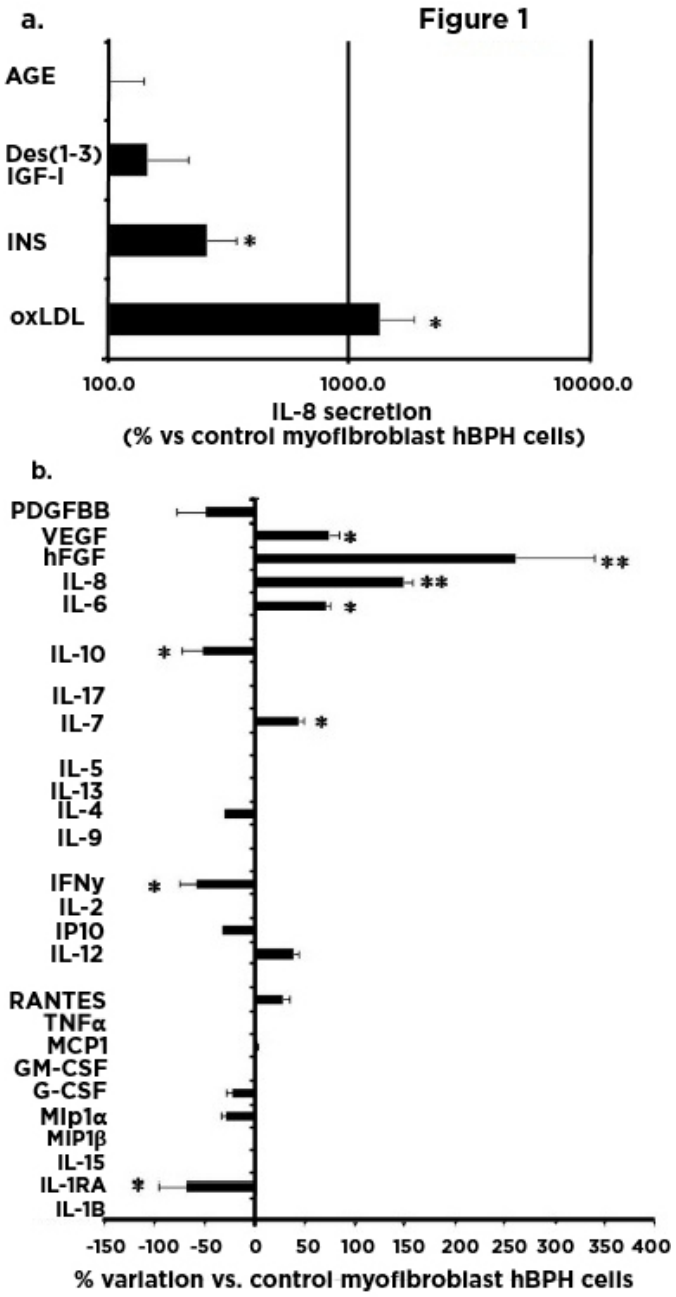

Figure 1. Panel a: Effect of different metabolic factors on IL-8 secretion by myofibroblast hBPH cells in a preliminary experiment.
Panel b: Effect of oxLDL treatment on cytokine/chemokine/growth factors secretion by myofibroblast BPH cells. (Adapted from Vignozzi et al.[10]).

MetS, 34 (12.5%) 4/5 and 6 (2.2%) 5/5.

Prostatic volume and AP diameter were significantly and positively associated with the number of MetS parameters, even after adjustment for age and 5-alpha reductase inhibitor's consumption (p=0.023 and p<0.0001, respectively). No correlation between MetS and the other diameters was observed (CC: p=0.198; LL: p=0.757). Patients fulfilling criteria for MetS (≥3 factors) had, on average, a prostate volume >60 cm3 (63 ± 27.39) and AP diameter >45 mm, those not fulfilling criteria had, on average, a prostate volume of 58cm^3. Among MetS parameters, only increased triglycerides and reduced HDL-cholesterol were associated with an increased risk of having a prostatic volume>60 cm3 (HR=3.268, p<0.001).

GD has been detected in 77/245 (31.4%) of cases. The presence of prostatic inflammation was demonstrated in all cases. The IS significantly increased as a function of MetS components (Figure 1), and patients with MetS had significantly a higher IS as compared to the rest of the sample (4.5±1.3 vs. 4.1±1.1; p=0.04). A significant positive correlation between the presence of MetS and the IS was observed (age and 5-alpha reductase inhibitor–adjusted HR: 1.250 [1.001–1.1561], p=0.049). Accordingly, each incremental unit of IS significantly increased the risk of having MetS, even after adjustment for age. Among MetS components, only dyslipidemia (reduced HDL cholesterol and elevated triglycerides) was significantly associated with elevated IS. Both IS and GD were correlated with total IPSS score, even after adjusting for age and BPH medical therapies (p=0.008 and p=0.050, respectively). In particular, a significant association between obstructive IPSS sub-scores and both IS (adj. r=0.166, p=0.011) and GD (adj. r=0.152, p=0.020) was observed, while irritative sub-scores were not correlated either with IS and GD.

Interestingly, we found that exposing myofibroblast hBPH cells to oxLDL (25 µg/ml, for 24 hours) significantly increased levels of a series of proinflammatory factors promoting BPH cell growth, such as IL-8, IL-6, bFGF, and VEGF. Secretion of the T cell growth factor IL-7 also significantly increased. Among the different factors, oxidised low-density lipoprotein (oxLDL) showed the highest secretion of IL-8 (>10-folds) – a surrogate marker of prostate inflammation – as well as IL-6, and bFGF (Figure 1 a and b).

DISCUSSION

These studies demonstrated the existence of an association among MetS features, prostate enlargement and prostate inflammation. We speculate that both conditions can have a relevant impact on LUTS severity in men with histologically proven BPH.

The progressive growth of the prostate in men with BPH, with the consequent modification of glandular profile into an oval, rounded shape, is mainly dependent on the increase of AP diameter.[16]

In our population of BPH men treated with simple

prostatectomy for severe LUTS, both prostate volume and AP diameter were progressively increasing as a function of MetS components. Interestingly, the fulfilling of the diagnostic criteria for MetS (simultaneous presence of at least three components) was associated with a pathological prostate volume and/or a pathological AP diameter. The strong association between MetS, in particular dyslipidaemia, and the AP diameter suggests that MetS is also associated with a modification of prostate shape which can lead to a compression of the prostatic urethra, with the consequent deterioration of voiding function.

A wealth of recent studies have indicated that prostate chronic inflammation is not only a common finding in BPH[17,18] but also plays a primary role in triggering prostatic cells overgrowth.[19-20] This notion mainly stems from preclinical studies, which have provided a great deal of information about an association between MetS and LUTS.

From a pathophysiological standpoint, dyslipidemia is the best recognised pro-inflammatory factor among all the others MetS features, leading to inflammation and pro-atherogenic remodelling of the vascular wall. Accordingly, among the metabolic factors tested (insulin, an IGF-1 analog, advanced glycation end product and oxLDL), only insulin and oxLDL induced a significant increase in IL-8 secretion, which was at least six-folds higher with oxLDL than with insulin. Interestingly, oxLDL was able to stimulate IL-8 secretion at a level similar to that achieved with TNFα, a well-known potent inflammatory trigger,[8,23] used in the study as positive control. This suggests that oxLDL could play a broad inflammatory effect on myofibroblast prostatic cells.

In our population, MetS was not only associated with an increased prostate volume and AP diameter, but also with a severe intraprostatic inflammation, and among MetS features, reduced HDL and increased triglyceride levels seem to be better predictors of prostatic inflammation than the other components of MetS. These observations substantiate the intriguing hypothesis that MetS could boost a chronic inflammation-driven prostate overgrowth. This is particularly relevant given that MetS is an emergent epidemic, and a potentially preventable or reversible, health condition.

Moreover, from a clinical point of view, the presence of a severe inflammatory pattern, leading to the disruption of the normal glandular arrangement, is the only determinant for a higher risk of LUTS deterioration.

CONCLUSION

The presence of MetS was associated with a substantial increase of prostate volume and a concomitant modification of prostate shape, associated with a selective increase of anterior posterior diameter. The presence of MetS, and in particular dyslipidemia, can be of importance for the development of a remarkable inflammation of the prostatic tissue, which could be a predictor, or even a driver, of BPH progression in men with severe LUTS.

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NEUROENDOCRINE TUMOUR OF THE PROSTATE: A RARE VARIANT

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ABSTRACT

About 95% of prostate cancers are adenocarcinomas. Neuroendocrine differentiation (NED) is seen in virtually all cases of prostatic carcinoma, mostly in a focal pattern. Extensive NED is associated to aggressive disease with a poor prognosis and most cases are diagnosed in advanced stages. We present a 79-year-old male who was admitted to our department with severe lower urinary tract obstructive symptoms and weight loss. On digital rectal examination, the prostate was fixed to the rectum with irregular margins. Serum prostate-specific antigen (PSA) level was 1.9 ng/ml. Transrectal ultrasound-guided prostate biopsies revealed small-cell carcinoma of the prostate. Multiple metastatic lesions in vertebral bones and iliac lymph nodes were detected by nuclear bone scan and abdominal computerised tomography CT. Thereafter, the patient was treated with cisplatin-based chemotherapy and palliative radiotherapy.

Keywords: prostate, prostate tumour, small-cell cancer.

INTRODUCTION

Cancer of the prostate (PCa) is one of the most important medical conditions facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer.[1] Furthermore, PCa is currently the second most common cause of cancer death in men.[2] In Turkey, PCa is the second common solid neoplasm after lung cancer in male population.[3]

Herein, we report a rare case of advanced stage pure small-cell prostate cancer, with diagnostic work-up and management.

CASE REPORT

A 79-year-old male admitted to our outpatient clinic with severe obstructive lower urinary tract symptoms and weight loss. His low urinary tract symptoms progressed particularly in the last six months. His medical history included presence of coronary artery disease and cholecyctectomy for gallbladder stone twenty years ago. His International Prostate Symptom Score (IPSS) was 27 and quality of life (QoL) score was 6. Uroflowmetry showed obstructed urine flow with peak flow rate of 8.3 ml/sec, average flow rate of 4.1 ml/sec with total voided

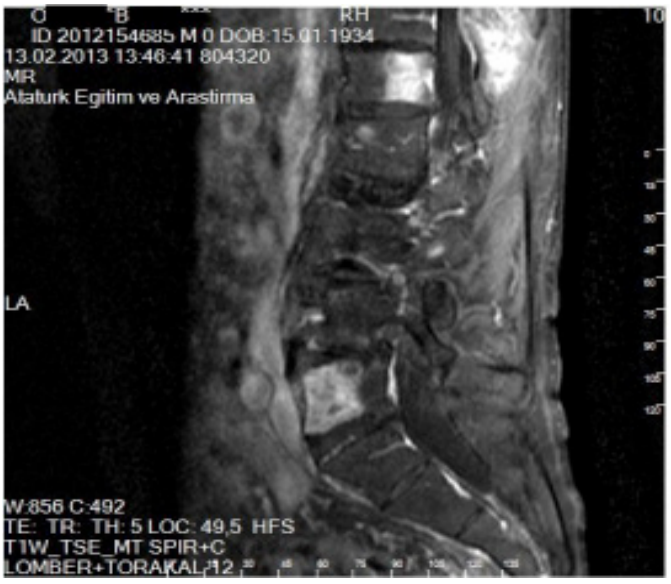

Figure 1. Abdominal computerised tomography showing multiple vertebral body metastases.

urine volume of 295 cc. Digital rectal examination (DRE) revealed a prostate including a stiff mass almost in all areas extending to the rectum with irregular margins. Serum prostate specific antigen (PSA) level was 1.9 ng/ml. Hypochromic anemia observed in complete blood count. Serum electrolytes and renal function tests were normal in blood biochemistry. Urine test was negative for urinary infection and for microscopic hematuria.

Urinary ultrasound showed normal kidneys without any hydronephrosis. We performed a 12-core transrectal ultrasound-guided prostate biopsy, and histopathological examination showed small-cell carcinoma of the prostate in all cores. Nuclear bone scan and abdominal computerised tomography (CT) demonstrated multiple vertebral metastatic lesions and enlarged iliac lymph nodes suggesting tumour metastasis (Figure 1). The thorax CT scan was within normal limits.

Patient was referred to the department of medical oncology and radiation oncology for further treatment. Cisplatin-based chemotherapy was administered with additional palliative radiotherapy for vertebral metastatic disease. During follow-up, serum creatinine levels elevated and the development of bilateral hydronephrosis detected on abdominal ultrasound as a consequence of local tumour infiltration of the ureters. Post-renal kidney failure was managed by inserting bilateral percutaneous nephrostomy. Currently, patient is on the sixth–month follow-up after the initial diagnosis.

HISTOPATHOLOGICAL EVALUATION

In histomorphologic examination, atypical cells with high nuclear-cytoplasmic ratio, having hyperchromatic granulations, hyperchromatic and irregular nucleus with fine granular chromatins invading the prostate gland was observed. Mitosis was a very common finding. Immunohistochemistry staining showed a diffuse positive staining of the tumour cells with synaptophysin, chromogranin and TTF-1 (Figures 2-5). Immunohistochemistry with Ki-67 staining was detected in more than 40% of the areas with tumour (Figure 6). No staining was observed by PSA. Due to WHO 2004 classification, these findings revealed a low differentiated neuroendocrine carcinoma of the prostate. The same histopathologic and immunuhistochemical findings were detected in all 12 cores of the prostate biopsy. Prostatic adenocarcinoma component was not observed in any of the cores.

DISCUSSION

Prostatic neuroendocrine differentiation has three distinct forms including focal neuroendocrine differentiation in prostatic adenocarcinoma, carcinoid tumour (well differentiated according to WHO classification) and small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma according to WHO classification).[4] Poorly differentiated neuroendocrine

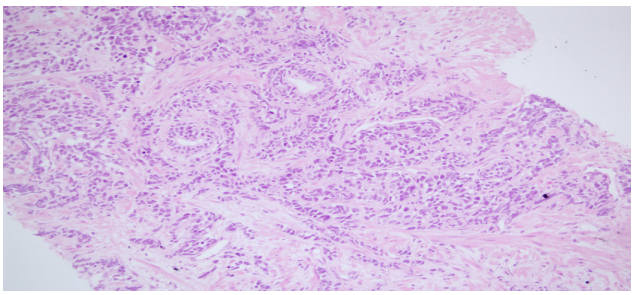

Figure 2. Atypical cells with pleomorphic nucleus invading the stroma between the prostate glands (H&E x200).

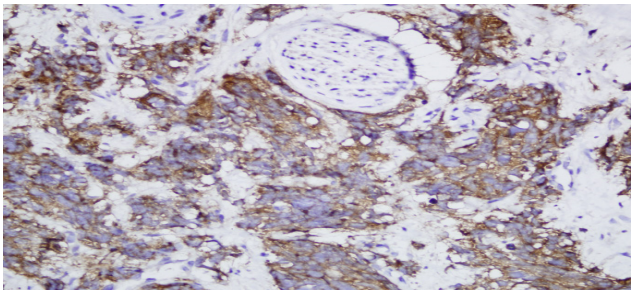

Figure 3. Diffuse chromogranin staining of tumour cells (x400).

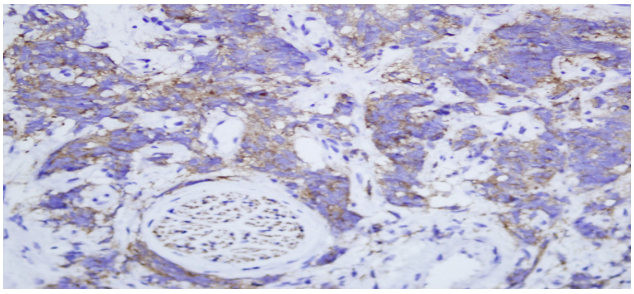

Figure 4. Diffuse positive staining of tumour cells with synaptophysin (x400).

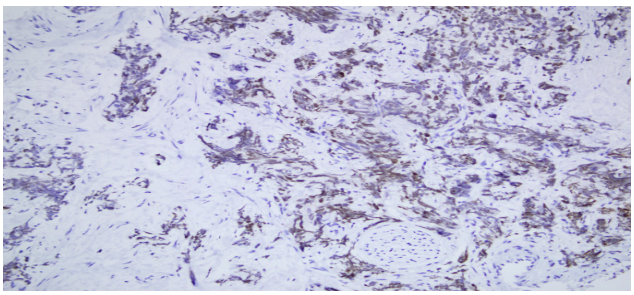

Figure 5. Diffuse positive staining of tumour cells with TTF-1 (x200).

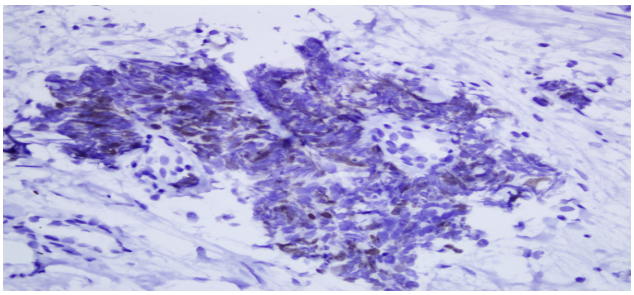

Figure 6. Diffuse positive staining of tumour cells with Ki-67 (x400).

carcinomas are detected up to 50% with prostatic adenocarcinoma.[4] However, in our patient, concurrent prostate adenocarcinoma was not detected in any of the 12 core prostate biopsies. In mixed tumours, neuroendocrine carcinoma components show positive staining with synaptophysin and chromogranin while they show negative staining for Papanicolaou (PAP) and PSA negative. Neuroendocrine carcinoma of the lung should be considered in differential diagnosis. In our case, immunohistochemical studies showed positive staining with TTF-1, which has a significant value in the differentiation from lung tumours.[5] In order to exclude the presence of lung cancer, a thorax CT was performed which revealed no lesion in the lung parenchyma. Therefore, our case was diagnosed as a primary prostate neuroendocrine tumour, which is a very rare entity.

Almost 95% of the prostatic neoplasms are adenocarcinomas.[6] Depending on the kind of technique used in detecting neuroendocrine cells, 10-100% of the prostate cancer tissues might involve neuroendocrine differentiation.[7,8] Histopathological forms include small-cell carcinomas,[9] carcinoids[10] and foci of neuroendocrine neoplastic cells in prostatic adenocarcinoma.[9,11] Extensive neuroendocrine differentiation (NED) is associated with hormone therapy refractory and aggressive disease.[12] This is of major importance because prostate cancers with NED have a poor prognosis (35% survival at 2 years) compared with cases where there are no neuroendocrine cells (97% survival at 2 years).[13,14]

Small-cell prostate cancer (SCPC) is a tumour with a tendency to systemically metastasise and thus has a poor prognosis. Even at the time of diagnosis, nearly 75% of patients are at advanced stage. SCPC has similar features with small-cell lung cancer.[15] It most commonly metastasises to the lymph nodes, liver, bone, lungs, pericardium, brain, rectum, and urinary bladder.[16] The number of patients reported is very limited in the literature. Therefore, the optimal therapy for SCPC has still to be defined. Extrapulmonary small-cell cancers are less sensitive to chemotherapy than pulmonary small-cell carcinomas. Although chemotherapy and radiotherapy may provide a cure in local disease, total treatment failure rate has been reported to be 84%.[17]

Elevated serum PSA is one of the most important tools in the diagnosis of prostate adenocarcinoma. However, in neuroendocrine tumours of the prostate, serum PSA levels might be within normal limits despite the patient having metastatic disease including systemic complaints such as weight loss, anemia and palpable tumour on DRE. In our case, serum PSA level was 1.9 ng/ml at the time of the diagnosis and our patient had multiple metastatic foci involving abdominal lymph nodes and vertebral bones. Therefore, DRE is very important in suggesting malignancy despite normal serum PSA levels as seen in our case.

CONCLUSION

In conclusion, neuroendocrine differentiation characterises the second phenotype by prevalence in comparison with prostate adenocarcinoma, but remains underdiagnosed. Neuroendocrine tumours cells are androgen-intensive and have a mitogenic effect on adjacent tumour cells. They are resistant to irradiation and chemotherapy. No standard therapeutic regimen exists, and the predicted survival is very short. Despite the fact PSA screening is highly valuable in detecting PCa; in highly aggressive PCa such as small-cell prostate cancer, serum PSA levels could be normal.

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PREDICTING REFRACTORY DETRUSOR OVERACTIVITY: ARE THERE ANY CLUES AT DIAGNOSIS?

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ABSTRACT

Approximately one-third of patients diagnosed with detrusor overactivity (DO) will be refractory to treatment with antimuscarinic drugs. In this study, we examined baseline clinical details and history of urinary tract infection (UTI), urodynamics parameters, urinary pH and ATP in voided urodynamic fluid for any prognostic factors that would allow prediction of the refractory state at the time of diagnosis. At follow-up (2 to 5 years), patients were characterised as responders or non-responders based on a >50% decrease in urge leaks and voids per 24 hours. Of the 61 patients who met the inclusion criteria, follow-up revealed that 25% of these did not respond to antimuscarinic therapy. There were no significant differences in urodynamic parameters in responders compared to non-responders. Patients with a greater number of leaks/week at baseline and a history of UTI were more likely to be non-responsive to antimuscarinic therapy. There was no difference in urinary pH or ATP concentration in voided urodynamic fluid in the two groups. The results indicate that severity of leakage at baseline history and a history of recurrent UTI appears to be poor prognostic features in patients with DO. These may be associated with the development of the 'refractory' state.

Keywords: Detrusor Overactivity, refractory, urinary tract infection, bacteriuria, adenosine triphosphate

INTRODUCTION

Overactive bladder (OAB) is a syndrome complex characterised by urge incontinence, that is, leakage with a severe urgent desire to urinate.[1] This debilitating condition affects approximately 17% of people over the age of 40,[2] with increasing economic consequences worldwide.[3,4] Urodynamic testing reveals detrusor overactivity (DO) resulting from involuntary contractions of the detrusor muscle during filling. The main treatment for DO is with antimuscarinic drugs, which are thought to work by interacting with muscarinic receptors located on the detrusor muscle or mucosa of the bladder.[5-7] Antimuscarinic therapy does not generally cure the condition but gives immediate benefit in about 65% of patients. Thus, 35% of patients do not respond to antimuscarinic therapy and are termed 'refractory', defined as failure to respond to detailed bladder training with more than two antimuscarinic agents for more than 12 months on frequency volume chart.[8] Poor outcomes were reported from a longitudinal follow-up of patients with DO (over a 5 to 10 year period) which found that long-term improvement was only achieved in 35% of women.[9] In addition, OAB symptoms have been reported to last for more than 10 years in 88% of patients with DO,[10] indicating that this is a disease syndrome with chronic implications for sufferers.

The underlying cause of DO has not been elucidated. Recent theories have focused on abnormalities in the purinergic signalling from the bladder urothelial cell layer, resulting in changes in afferent nerve impulses from the bladder that increase the sensation of 'urgency'. Increased release of adenosine triphosphate (ATP) from the bladder urothelium has been demonstrated in conditions of bladder dysfunctions characterised by pain, such as painful bladder syndrome (including interstitial cystitis).[11-12] In 2010, we examined the release of ATP into intravesical fluid from patients with DO at urodynamic testing.[13] We found a correlation between the first desire to void (FDV) and the concentration of ATP present in the intravesical fluid.[13] Similarly, we have

recently reported that intravesical ATP concentration correlates with the FDV in patients with OAB syndrome (without urodynamically proven DO).[14] Taken together, these studies indicate a role for ATP in bladder sensation. However, whether the magnitude of ATP release during bladder filling can predict treatment response has never been studied.

Several recent studies have described high rates of bacteriuria (25-40%) in women with urodynamic refractory DO[15] and a wider group with clinical overactive bladder (OAB) syndrome.[16-17] Despite this, infection has largely been ignored as a contributor to the aetiology of refractory DO.[18] The aims of the current study were to evaluate patient response to antimuscarinic therapy in relation to 1) patient history of bacterial cystitis at the first visit and 2) ATP concentration in voided urodynamic fluid at baseline urodynamics.

METHODS

Patients who had presented for urodynamic testing between January 2008 - April 2011 at our regional Department of Urogynaecology who had been recruited into a study of ATP levels in voided urodynamic fluid (n=118)[13] were considered for this study. Three weeks prior to urodynamics testing patients had an initial visit when history was taken together with screening mid-stream urine for detection of bacterial cystitis. Any patients with a positive result for bacterial cystitis were treated with appropriate antibiotics before urodynamics was performed. Only patients who were not symptomatic for urinary tract infection (i.e. absence of foul-smelling urine and dysuria) were eligible for urodynamics. Patients who had a urodynamic diagnosis of idiopathic DO, that is involuntary detrusor contractions during the filling phase which were either spontaneous or provoked (n=61), were followed-up. Patients who were either urodynamically normal or pure urodynamic stress incontinence with no urge symptoms were excluded from this follow-up study as treatment response would not equate to antimuscarinic efficacy (n=48). Patients with neurological disorders (n=1), any voiding dysfunction (n=2), or previous deep pelvic radiotherapy (n=3) were excluded. In addition, women who were unable to receive antimuscarinics (i.e. Dementia/Glaucoma n=3) were also excluded.

Following urodynamic diagnosis patients with idiopathic DO received routine clinical care including bladder training and antimuscarinic therapy. Patient response to antimuscarinic therapy was determined by frequency volume chart (urge leaks and voids per 24 hours, nocturia). 'Response' was denoted as greater than 50% benefit on urge leaks and voids per 24 hours. Additional patient history was recorded, including age, duration of symptoms, menopausal status, number of pregnancies/births, number of antimuscarinic agents tried, and urodynamic parameters. Comparison of findings in responders compared with non-responders was undertaken using a Mann-Whitney test.

Table 1. Clinical history for patients with DO characterised as responders or non-responders.

	Responders (n=37)	Non-Responders (n=11)	Significance
Age (range)	66.00 (32-92)	66.50 (33-87)	NS
Leaks/week (IQR)	7 (3-18)	21 (12-29)	p=0.014
Post menopause (%)	78%	83%	NS
Pregnancies (range)	3 (0-6)	3 (0-5)	NS
Births (range)	2 (0-6)	3 (0-5)	NS
UTI ever	48.5%	91%	p=0.015
Any recurrent UTI	21%	63.5%	p=0.013
No history of UTI	46%	8%	p=0.01
Duration of symptoms (range, years)	6.38 (2-29)	7.83 (2.5-25)	NS
Number of antimuscarinic drugs tried (range)	1 (1-4)	2.5 (2-7)	p=0.0026

Patient history of bacterial cystitis was defined as either 'recurrent UTI' which was more than 3 proven episodes of infections in 5 years;[19] "any UTI", that is any proven UTI during the patient's adult life, or no history of UTI. Comparison of the prevalence of UTI in responders and non-responders was undertaken with a chi-squared test. In addition, laboratory findings of urinary pH and concentration of ATP in voided urodynamic fluid was collated and compared by Mann-Whitney U test. Because a correlation between ATP in voided urodynamic fluid and the FDV has previously been reported,[13] we also examined this relationship in the responders and non-responders using linear regression. All statistical analyses were undertaken using GraphPad Prism (version 6).

RESULTS

Of the 118 patients who had ATP determinations at the time of their diagnosis, 61 met the inclusion criteria. Nine patients were lost to follow-up (despite contacting the GP) and three were completely non-compliant with therapy, thus 49 patients underwent treatment and could be traced. Follow-up revealed that 37 of these (75%) had responded to antimuscarinic therapy and 12 (25%) were non-responders. The follow up period for this study was ranged from 2 to 5 years.

In examining the clinical history (collected at first presentation) there were no significant differences between responders and non-responders in relation to age, parity, menopausal status, or duration of symptoms (Table 1). However, baseline severity of leakage gave some significant prognostic information in that severity of leakage was greater in non-responders (median 21 leaks/week) compared to responders (median 7 leaks/week, p=0.01, Mann-Whitney, Table 1). Interestingly, there was a difference between UTI history and the clinical outcome (p<0.0001, chi-square). A significantly higher percentage of the non-responders had a history of both recurrent UTI (p=0.013, Mann-Whitney) and any UTI episode (p=0.034, Mann-Whitney, Table 1) while a significantly higher percentage of responders had no UTI history (p=0.0005, Mann-Whitney, Table 1). The non-responders had been treated with a median of 2.5 antimuscarinic agents (ranging from 2 to 7). This was significantly greater than the number of antimuscarinic agents than the responders had been treated with (p=0.03, median 1, range 1 to 4, Table 1).

Table 2. Patient data collected at urodynamic diagnosis (Median, IQR).

	Responders (n=37)	Non-	Significance
First desire to void (FDV, mL)	170 (135-235)	190 (130-260)	NS
Maximum Cystometric Capacity (MCC, mL)	410 (312-492)	417 (367-473)	NS
Maximum Detrusor Pressure (pDET, mm Hg)	35 (24-45)	42 (27-55)	NS
Urinary pH	6.41 (5.53-7.02)	5.98 (5.54-6.33)	NS
ATP concentration (nM)	2.4 (0.6-14.9)	2.95 (1.5-5.88)	NS

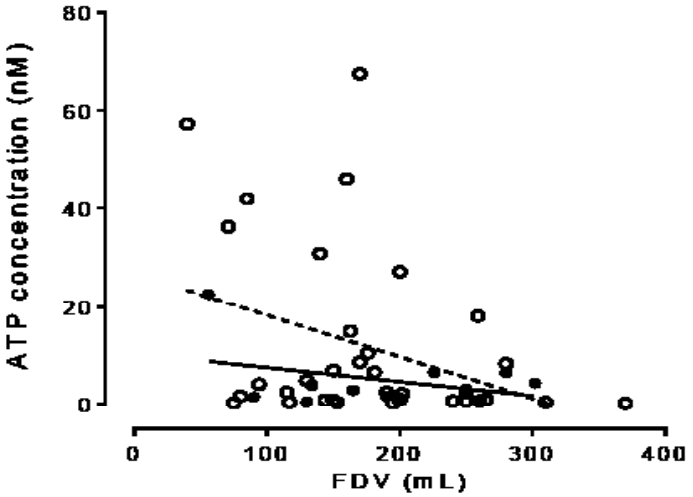

Figure 1. Correlations between ATP concentration in voided urodynamic fluid and FDV in patients with DO who respond to antimuscarinic therapy (open circles, p=0.039) and in patients who are non-responders (p=0.25, closed circles).

In examining urodynamic parameters of responders compared to non-responders there was no significant difference between FDV, maximum cystometric capacity (MCC) and maximum detrusor pressure (Table 2). The ATP concentration in voided urodynamic fluid did not differ between responders and non-responders (Table 2). A significant correlation between ATP in voided urodynamic fluid and FDV (Figure 1) was seen in the responders (p=0.039, r^2=0.12) but not in the non-responders (p=0.25, r^2=0.14).

Urodynamic parameters and ATP concentration in voided urodynamic fluid was also analysed in relation to patients who had a history of UTI (n=31) and those with no proven episodes of infection (n=18). In this instance there was again no significant difference in FDV, MCC and

	UTI (n=31)	No history of UTI (n=18)	Signifi-cance
First desire to void (FDV, mL)	167 (133-250)	193 (121-232)	NS
Maximum Cystometric Capacity (MCC, mL)	389 (300-440)	422 (365-500)	NS
Maximum Detrusor Pressure (pDET, mm Hg)	40 (26-45)	32 (20-55)	NS
Urinary pH	6.255 (5.5-6.49)	6.46 (5.45-7.05)	NS
ATP concentration (nM)	3.9 (1.4-10.4)	0.9 (0.36-4.66)	p=0.049

Table 3: Effect of a history of UTI on urodynamic parameters (Median, IQR)

maximum detrusor pressure (Table 3). However the ATP concentration in voided urodynamic fluid was significantly higher in patients with a history of UTI (p=0.049, Mann-Whitney, Table 3).

DISCUSSION

In this study we have found that both baseline severity of leakage and history of UTI are important prognostic features. Increased severity of leakage was seen in patients who were not responsive to antimuscarinic therapy. Similarly, Morris and associates reported in 2008 that severe urge incontinence at presentation was associated with treatment failure,[9] although the cause of this leakage has not been determined.

For the past 30 years, the possible role of subclinical infection/inflammation in the etiology of DO has largely been ignored. A number of studies have reported an increased prevalence of bacteriuria in patients newly diagnosed DO.[20-23] Similarly, bacterial cystitis has been described in patients with OAB syndrome, who had not had urodynamics.[17] Thus several authors have now shown that the incidence of bacteriuria/bacterial cystitis is more common in new onset DO (or incontinent women with OAB) than in controls, although a relationship between cystitis and refractory DO has not previously been reported.

In this study we report that the likelihood of a patient having a history of recurrent UTI was three-fold greater in patients who failed to respond to antimuscarinic therapy (non-responders) compared to those who respond to therapy. Thus, our results suggest that recurrent UTI, or indeed a history of UTI, may have importance in the acquisition of a 'refractory' state. In the last 2 years there have been two preliminary studies of antibiotic therapy in patients with OAB. In both trials, antibiotic therapy (in combination with antimuscarinic drugs and bladder training[24]) or antibiotics alone[25] was seen to significantly improve the treatment response, as indicated by a reduction in voids per day[24-25] or urgency scores.[25]

One proposed mechanism is that bladder inflammation, associated with bacteriuria, evokes increased afferent nerve activity in response to bladder distension.[26-28] Patients with refractory DO have been found to have increased expression of nociceptive neuropeptides such as substance P.[29] Similarly, nerve growth factor (NGF) is increased in biopsies and urine of refractory patients.[30] In addition to NGF, elevated levels of pro-inflammatory cytokines have been reported in OAB patients.[31-32]

The second aim of this study was to determine if the ATP concentration in voided urodynamic fluid was able to prognosticate the response to antimuscarinic therapy. Our results indicate that this was not the case, with ATP concentration in voided urodynamic fluid not being able to be used as a useful biomarker to predict response to antimuscarinic therapy for patients with DO. It is of interest that the previously observed correlation between FDV and ATP in voided urodynamic fluid[13] was preserved in the patients who responded to antimuscarinic therapy, but was lost in the non-responders, although it is likely that this is related to the small number of patients in the latter group (n=12). Also of interest is the finding that the ATP concentration in voided urodynamic fluid from patients with a history of UTI is significantly higher (p=0.049) than that in patients who had no history of infection. This is in contrast to our findings of decreased ATP in patients with a current bacterial infection.[33] It is possible that a history of infection alters the long-term response of the urothelium to stretch, leading to increased release of ATP as opposed to a current infection decreasing ATP release possibly through a decrease in urothelial cell viability.[34] These differences in ATP release in patients with a current infection and a history of infection need to be further investigated to fully understand the way in which infection alters urothelial responses.

CONCLUSION

Results from this study indicate although ATP remains an important molecule for the signalling of afferent impulses in the urinary bladder, it is not useful as a prognostic indicator for responsiveness to antimuscarinic therapy. Severity of leakage at baseline history and a history of UTI appears to indicate a poor prognostic significance in patients with DO possibly being associated with the development of the 'refractory' state.

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FEMALE SEXUAL DYSFUNCTIONS AND UROGYNECOLOGICAL DISORDERS

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ABSTRACT

Female sexual dysfunctions are a highly prevalent and often-underestimated health problem and include disorders of sexual desire, arousal, orgasm and sexual pain, associated with self-distress. Pathophysiology of female sexual dysfunctions is complex and still poorly understood, although it has been related to several biological, medical and psychological factors. Amongst women, urogynecological disorders such as urinary incontinence, overactive bladder syndrome, bladder pain syndrome and pelvic organ prolapse, have been found to be associated with sexual dysfunctions, although the biological and psychological bases of these associations are poorly investigated. Data on sexual function impact of these conditions come from several cross-sectional or community-based, epidemiological studies based on self-administered validated psychometric tools. This review focuses on the most relevant available evidence on the impact of urogynecological disorders and related surgical treatments on female sexual function.

Keywords: bladder, pain syndrome, female sexual dysfunctions, LUTS, pelvic organ prolapse, urinary incontinence.

INTRODUCTION

Sexuality is one of the most important components of quality of life (QoL) in both sexes. Female sexual dysfunctions (FSD) have been recognised as a common problem and its prevalence increases dramatically with increasing age.[1] Data from the National Health and Social Life Survey (NHSLS) revealed sexual dysfunctions have a higher prevalence in women (43%) than men (31%).[2]

Several studies reported that female sexual function (FSF) is negatively influenced by lower urinary tract symptoms (LUTS) and pelvic floor disorders (PFD).[3-6]

The importance of these observations is related to the high and increasing incidence worldwide of urogynecological conditions.[7-8] Thus, all physicians dealing with women's health should be aware of the possible detrimental effect of these conditions on FSF.

The aim of this article is to review the published data on the impact of urogynecological conditions on FSF, focusing on urinary incontinence (UI), overactive bladder syndrome (OAB), pelvic organ prolapse (POP) and bladder pain syndrome/interstitial cystitis (BPS/IC).

DEFINITION AND MEASURES

The second International Conference of Consensus on Women's Sexual Disorders[9] classified the FSD in four categories: sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Because the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR defines FSD as "disturbances in sexual desire and in the psycho-physiological changes that characterise the sexual response cycle and cause marked distress and interpersonal difficulty",[10] both sexual function and sexually-related personal distress should be considered when assessing FSD. Although some studies estimate that 40–50% of women report at least one sexual complaint,[11] not all sexual complaints lead to dissatisfaction or sexual distress and, until recently, most research on FSF has focused on sexual complaints but has not considered the QoL impact of these complaints in relation to sexual distress.[12]

The self-administered questionnaires are a reliable standardised method for clinical evaluation of FSF.[13-22] Questionnaires are also an ideal research tool to assess outcome from various treatment modalities and can be of use in epidemiological surveys. Most of the published

studies have investigated FSF using the Female Sexual Function Index (FSFI)[18] or the POP/UI Sexual Questionnaire (PISQ).[19] The FSFI is a 19-item questionnaire that features six areas of sexual function: desire, arousal, lubrication, orgasm, satisfaction and pain. The PISQ includes 31 items and assesses sexual function in women with POP and/or UI. Their abbreviated forms have a wider applicability in the clinic to minimise the time of administration.[20] The International Continence Society (ICS) provided a validated questionnaire, the ICIQ-Female Sexual Matters associated with Lower Urinary Tract Symptoms (ICIQ-FLUTSsex), which is useful for researchers and clinicians in both primary and secondary care institutions to obtain a brief, yet comprehensive, summary of female sexual matters and the impact of urinary symptoms on this.[21]

Up until now there have been reported no standardised values for what should be considered a 'normal' sexual function and the majority of studies show the changes in the overall score over time. However, average values of the women with and without LUTS and UI have recently been reported for the FSFI.[22]

UI AND OAB

Prevalence rates of FSD in women with UI are estimated to range between 26–47%.[23-25] All forms of UI are associated with FSD of all phases of the sexual cycle and studies have examined the impact of UI on individual domains of sexual function and satisfaction.[26-31]

The loss of urine significantly impairs the QoL of women, who are forced to organise exhausting strategies to prevent or mask stains and/or odours.[32] At emotional and behavioural levels, a generalised apathy, feelings of guilt and depressive attitude may develop to different areas of life due to the unpredictable nature of the symptoms.[33] Thus, several studies showed a correlation between UI and major depression, which has a three times higher incidence in incontinent patients than in continent patients.[34] Specifically, women with UI feel threatened in their femininity, expressing feelings of shame, inadequacy and reduced self-esteem[35-37] and subsequently a communicative and emotional inability with a strong sense of isolation.[38] The lack of libido and reduced level of self-esteem because of a fear of uncontrolled leakage are the main factors in women with UI and FSD.[39]

Nilsson et al.[40] evaluated women with UI and/or urinary urgency (the key symptom of OAB) and their partners and reported that 22% of the men and 43% of the women stated that the female urinary symptoms impaired their sexual life. 49% of the women expressed worries about having urinary leakage during sexual activity, but 94% of their male partners did not. 23% of the men and 39% of the women responded the woman leaked urine during sexual activity and the majority (84%) of women considered this a problem, yet 65% of their partners revealed they did not.

Focusing on sexual distress, Knoepp et al.[41] assessed sexual complaints among 305 women seeking outpatient gynecologic care using the Female Sexual Distress Scale (FSDS). 26% of the scores reflected distress, and distressed women were more likely to be younger, have higher depression scores and report decreased arousal, infrequent orgasm, and dyspareunia. Women with sexual distress were also more likely to report sexual difficulty related to pelvic floor symptoms, including UI with sexual activity, sexual avoidance due to vaginal prolapse, or sexual activity restriction due to fear of UI.

Salonia et al.[42] found that 47% of patients who reported a hypoactive sexual desire had stress UI (SUI), and 46% of those who reported orgasm problems also had significant symptoms of OAB with urgency UI (UUI). The study concluded that patients with UI or LUTS more frequently suffer from sexual dysfunction compared to healthy control patients. Accordingly, Yip et al.[43] found that patients with SUI or OAB have a decreased QoL measured with King's Health Questionnaire (KHQ),[44] less sexual satisfaction and worse marital relations than controls. In the study of Coksuer et al.,[45] patients with a diagnosis of mixed urinary incontinence (MUI) had significantly lower mean PISQ-12 scores than the ones with SUI and urodynamic detrusor overactivity (DO) whereas patients with SUI had lower mean PISQ-12 scores than patients with DO, so they concluded that MUI has the greatest impact on sexual function when compared with SUI and DO alone. Sacco et al.[46] reported that, among women with UI and/or OAB, those with UUI and MUI reported worse FSD as compared with those with SUI or with dry OAB. Women with urodynamically-proven detrusor overactivity incontinence appeared in this and other studies to have the worst FSF.[43,47-48] Mechanisms associated with the impact of OAB on FSF can be the fear of leakage during stimulation and intercourse, coital UI during orgasm, the need to interrupt intercourse to void, urgency and frequency after coitus, dyspareunia and pelvic floor dysfunction.

The fear of urine leakage during intercourse was found in 11-45% of patients with UI.[49-54] Moran et al.[53] found that 11% of 2,153 women had UI during intercourse, most of which reported this symptom only in a questionnaire, 70% reported urine leakage during penetration, 20% only during orgasm and 11% during both penetration

and orgasm. A SUI was present in 80% of women with UI during penetration, in 93% of women with UI during orgasm and in 92% of women with UI during both phases. The pathophysiology leading to UI during intercourse is not clear. During penetration, the displacement of the anterior wall of the vagina and bladder neck or the increase of the intra-abdominal pressure loss can cause SUI. Detrusorial simultaneous contractions and urethral relaxation were demonstrated in urodynamic studies during orgasm.[51]

Recent studies evaluated the relationship between body mass index (BMI), UI and FSD among perimenopausal and postmenopausal[55] or overweight and obese women,[56-57] showing that UUI and SUI are more common and have greater impact on sexual function in obese women. Furthermore, increased BMI early in menopause represents a risk both for UI and for FSD although the severity of the FSD may not be directly related to the severity of UI or obesity.

SURGERY FOR UI

Although SUI surgery is thought to improve sexual function,[39,58-59] data reporting sexual function following surgical repair are limited and conflicting.[60]

Moran et al.[61] evaluated 55 women with SUI and coital incontinence treated with Burch colposuspension. Before the procedure, 36 women (65%) had coital leakage only with penetration, 9 women (16%) had only with orgasm and 10 (18%) with both. After the procedure, 81% described no further coital incontinence. In Baessler,[62] a cohort of sexually active women were affected by SUI with concomitant coital incontinence, this problem was cured in 70% of patient and improved in almost 7% after Burch colposuspension. Brubaker et al.[39] studied sexual function in 655 women randomised to Burch colposuspension or sling surgery and reported patients with successful surgery had a greater improvement in PISQ-12 scores in both Burch and sling groups.

Berthier et al.[63] found no significant postoperative changes regarding frequency of sexual intercourse, satisfaction with sexual intercourse or personal importance of having an active sexual life in 66 women undergoing tension-free vaginal tape (TVT) procedure for SUI. These results are in agreement with those of previous studies.[64-66] Ghezzi et al.[67] reported that 62.2% of women undergoing TVT procedure had no change in sexual function after surgery, no significant difference in the incidence of dyspareunia and two patients (3.8%) referred intercourse to be worse, one because of erosion and one for 'de novo' anorgasmia.

Studies on trans-obturatory sling (TOT) reported no impact or a beneficial effect of this procedure on FSF.[68-70] Filocamo et al.[68] included in their study women complaining of urodynamic SUI who were both sexually and non-sexually active at baseline. 105 women out of 133 had a TOT procedure, while 28 out of 133 had a retropubic procedure. Twelve months after surgery, 22 out of 54 non-sexually active women (40%) re-established sexual activity, whereas only 6 out of 79 (7.5%) patients, sexually active at baseline, were not sexually active one year after surgery. The authors concluded that after a sling procedure, FSF improves and a very relevant percentage of non-sexually active women can recover sexual activity after sling. Accordingly, Xu et al.[70] evaluated sexual function before and six months after a TOT procedure in 55 sexually active women. More than half (54.5%) the women reported an improvement in sexual function after surgery and 45.5% reported no change, and no statistically significant difference was found between preoperative and postoperative total or domain scores on the FSFI, so they concluded that TOT procedure did not significantly affect sexual function. In a recent study, Zyczynski et al.[71] described an increase of mean PISQ-12 scores after mid-urethral sling surgery (TOT and TVT) and a reduction of dyspareunia, incontinence during sex and fear of UI during sex.

However, surgeons should know that vaginal sling procedures may have a potential negative effect on FSF due to damage to vascular and/or neural genital structures or to 'de novo' dyspareunia. Baessler et al.[72] reported that dyspareunia was a severe indication for removing the posterior intravaginal synthetic sling. Bekker et al.[73] described the autonomic and somatic pathways in relationship to sling surgery in 14 adult female dissected hemipelves, after TVT or TOT procedures have been performed. They concluded that the dorsal nerve of the clitoris was not disturbed during the placement of the TOT but the autonomic innervation of the vaginal wall was disrupted by the TVT procedure, which could lead to altered lubrication-swelling response.

PELVIC ORGAN PROLAPSE

Several studies investigated the specific role of POP on FSD, with conflicting results. Intuitively, POP would seem likely to have an adverse impact on sexual function; however, older age and postmenopausal status, common in women with prolapse, are also associated with sexual dysfunctions and may confound the association between

POP and FSD.[74-75]

In a recent cross-sectional observational study, Athanasiou et al.[76] evaluated the effect of POP on FSF in 101 women compared with 70 women without POP, and found that FSF was worse in POP group than in control group, but did not seem to worsen with an increasing grade of POP. Based on a linear regression model, they concluded that the presence of prolapse only partly explained impaired sexual functioning in women with POP. Investigating 495 women scheduled for hysterectomy with evidence of PFD, Handa et al.[77] found that UI was significantly associated with low libido, vaginal dryness, and dyspareunia and independent of age, educational attainment and race, but POP was not associated with any sexual complaint. Barber et al.[47] reported 81% of sexually active patients described sexual intercourse as 'somewhat' or 'very' satisfactory, and that neither UI nor POP significantly influenced the answer to this question. Weber et al.[50] reported women with POP and/or UI have a similar sexual function than women without these PFD. In this study, increasing age was the only significant factor predictive of FSD, and increasing grade of POP predicted interference with sexual activity, without affecting frequency of intercourse or description of satisfaction with the sexual relationship.

On the other hand, Novi et al.[78] compared sexual function of women with POP to that of women without POP using the PISQ, and reported that mean PISQ score in sexually active women with POP were significantly lower compared to controls, with significant difference in satisfaction with sexual relationship, actual frequency of intercourse and ability to achieve orgasm with masturbation, but no difference in the desired frequency of intercourse, initiation of sexual activity, rate of anorgasmia or subjective assessment of partner satisfaction. The study of Digesu et al.[79] reported a comparison of prolapse symptoms and QoL with physical examination findings and urinary, bowel and sexual dysfunctions in symptomatic and asymptomatic women. They identified women as symptomatic from prolapse if they complained of any of the prolapse symptoms and/or on direct questioning the patients reported a "sensation of dragging" or "a lump or fullness in the vagina". These symptoms were correlated with anterior, posterior and apical compartment prolapse severity. For the symptomatic women only, sexual symptoms severity was correlated with apical and posterior wall prolapse, so they concluded that FSD was related to uterine displacement, likely leading cervix to obstruct penile penetration. Displacement of the uterus coming down, pulling the ligaments, pedicles and peritoneum may also lead to a sensation of heaviness or "dragging" vaginal feeling, which may interfere with sexual function.

POP SURGERY

Functional results are as important an outcome measure as anatomical results in the assessment of pelvic floor surgery.[80] Sexual function in particular has been overlooked and superficially assessed in the past and several studies of the impact of surgical intervention have also been limited by absence of baseline data.[81] Based on data from the Colpopexy and Urinary Reduction Efforts (CARE) study,[82-83] Handa et al.[74] administered the PISQ-12 to 224 sexually active stress-continent women planning abdominal sacrocolpopexy for stage II-IV prolapse, before and one year after the intervention. In the CARE trial, concomitant Burch colposuspension was randomly assigned at the time of sacrocolpopexy, and posterior colporrhaphy was performed at the discretion of the surgeon, so the potential impact of those procedures on postoperative sexual function was assessed. One year after colposacropexy, the number of sexual active women rose significantly from 148 (66.1%) to 171 (76.3%), the number of women who avoided sex because of vaginal bulging decreased from 103 (47.3%) to 10 (4.6%) and the mean PISQ-12 score among women who were sexually active before and after surgery improved significantly. 58% of women with dyspareunia at baseline did not report pain during intercourse after surgery and 14.5% of women without dyspareunia reported pain one year after sacrocolpopexy, regardless of concomitant Burch colposuspension. The proportion of women with infrequent sexual desire, sexually excited during sexual activity and who reported orgasm with intercourse did not change substantially. Only 11 of 148 women who were sexually active before surgery became inactive after surgery. They did not differ in age or preoperative prolapse severity from women who continued sexual activity after surgery and reported no postoperative sexual interference from fear of incontinence, vaginal bulging or pain. However, more of these women reported infrequent sexual desire after surgery. Comparing Burch colposuspension group versus non-Burch group, they did not find difference in proportion of sexually active women, dyspareunia and PISQ-12 scores one year after surgery, while more women who underwent posterior repair reported postoperative dyspareunia, although the difference did not reach statistical significance. These data are consistent with previous studies reporting a high percentage of dyspareunia after posterior repair, both with levator ani muscle plication narrowing of mid-vagina[84-86] and with posterior colporrhaphy.[87-88] The authors

concluded that most sexually active women can expect to continue sexual activity following sacrocolpopexy and experience less impact from pelvic floor symptoms.[74]

The presence of prosthetic material in the vagina may adversely affect sexual function, although several studies reported contradictory results. Wang et al.[80] evaluated the short-term impact (six months) of surgical repair with total transvaginal mesh (TVM) on FSF among 27 sexually active women with symptomatic POP. In these patients the TVM surgery corrected the pelvic anatomy and urinary symptoms successfully; while there were no significant changes in sexual desire, sexual arousal, orgasm, satisfaction, the mean postoperative score of the lubrication and dyspareunia domains worsened significantly, with two-thirds of all participants showing a lower total FSFI score postoperatively. The authors explained that changes in vaginal blood flow and ischemia, disruption of the dense nerve innervation of the anterior and lateral vaginal wall during dissection and the insertion of permanent mesh in the vagina might have contributed to the painful sensation and loss of lubrication postoperatively. Similar results were obtained by other studies.[89-90] On the other hand, Hoda et al.[91] reported an initial deterioration of sexual function during the first three months after transobturator mesh implants, followed by a steady improvement that reached a significant difference at twenty-four months postoperatively and Dwyer and O'Reilly[92] reported a significantly decreased dyspareunia in 97 women with recurrent or large POP undergoing polypropylene mesh repair to reinforce anterior and posterior compartment after six, twelve and twenty-four months.

Lowestein et al.[93] evaluated sexual function, prolapse symptoms and self-perceived body image after treatment for POP to explore differences in body image perception and sexual function following conservative and surgical treatment for POP. At six-month follow-up visits, the patients reported significant improvement in FSF from baseline in both groups and the improvement in FSF, as measured by PISQ-12, was not significant among sexually active patients treated with a pessary compared with those treated surgically. In this study, body mass index and changes in body image perception were the only independent factors associated with changes in PISQ-12 score following POP treatment.

BPS/IC

Sexual dysfunction issues have been reported among women with BPS/IC and can contribute to reduced QoL in these patients. Pelvic pain due to inflammation of the bladder wall and neuropathic dysfunction, dyspareunia, and fear of pain during intercourse are particularly frequent among these patients and may cause resistance to penetration and consequent pelvic floor overactivity, vulvodynia, and vaginismus.[94]

Sacco et al.[46] showed that, among women with lower urinary tract disorders, those with BPS reported the greatest adverse impact on FSF, mostly because of sexual pain, followed by those with urodynamic DO, clinical diagnosis of UUI, MUI and SUI, dry OAB and voiding-phase LUTS.

Accordingly, Peters et al.[95] sent a mailed survey to 5000 randomly selected women from the United States (controls) and 407 women with IC (cases) from a large referral centre, including the Female Sexual Distress Scale (FSDS) and questions about sexual function, desire, orgasm, and pain. A significantly greater proportion of cases reported fear of pain and pain with intercourse. In adulthood, a large proportion of cases reported pelvic pain, fear of pain during intercourse, and dyspareunia. Furthermore, after the diagnosis of IC, the number of cases reporting moderate to high desire and orgasm frequently and very frequently declined significantly.

Verit et al.[96] evaluated 112 women complaining of chronic pelvic pain (CPP) with a comprehensive history, including FSFI, compared with a group of 108 healthy women without CPP. Among 112 CPP patients, 78 (69.6%) of them had FSD and 34 (30.4%) patients did not have FSD in this study. Among patients with FSD, 42 patients (53.8%) had hypoactive sexual desire disorder, 26 patients (33.3%) had sexual arousal disorder, 17 patients (21.7%) had orgasmic disorder and finally 58 patients (74.3%) had sexual pain disorder. In compliance with these findings, using FSFI to compare FSD in 75 patients affected by IC with 22 controls, Ottem et al.[97] reported that total adjusted FSFI scores differed between patient and controls and that 51 patients (68%) had an abnormal FSFI score versus 3 controls (14%), concluding that patients with IC have sexual dysfunction, including pain, dyspareunia, sexually related distress and significant declines in desire and orgasm frequency, more commonly than do controls.

In a survey of 1469 women who met criteria for BPS/IC diagnosis, 88% of those with a sexual partner reported ≥1 general sexual dysfunction symptom and 90% reported ≥1 BPS/IC-specific sexual dysfunction symptom in the past four weeks.[98] In the multivariate models, BPS/IC-specific sexual dysfunction was significantly associated with more severe BPS/IC symptoms, younger age, worse depression symptoms, and worse perceived general health. Of note, only a small proportion (about 10-20%) of those

women with sexual dysfunction sought medical help for the condition.

CONCLUSIONS

Sexual dysfunctions are common health issues in women suffering from urogynecological disorders and have a great impact on quality of life. However, findings of published studies are often conflicting, particularly on the role of POP. Data on the relative impairment of sexual function in women with different types of urogynecological disorders are deficient. The consistency of published studies is often limited by several biases such as use of non-condition-specific instruments, lack of a control group and of urodynamic evaluation.

The diagnosis of FSD requires a complete anamnesis with regard to the sexual history, and self-administered questionnaires represent useful tools not only for research but also for patient-clinician discussions on sexuality.

Although urogynecological surgery is thought to improve sexual well-being, data reporting sexual function following surgical repair are still limited and often diverging. More research is needed using standardised assessment tools to define clear endpoints in this field.

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LOWER POLE CALYCEAL STONE AND LITHOTRIPSY - ARE ISSUES WITH CLEARANCE FACT OR REALITY?

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ABSTRACT

The lower pole calyceal (LPC) stone continues to be an enigma. The complex anatomy of the lower pole collecting system, along with other factors like acute pelvi calyceal angle and narrow and long infundibulum, are some of the complicating factors affecting stone clearance. There have been many studies assessing the impact of collecting system anatomy and most conclude that the complex anatomy of the lower pole collecting system does impact the overall stone-free rate.

Keywords: kidney stones, lower pole calyceal (LPC), percutaneous nephrolithotomy (PNL), urolithiasis

INTRODUCTION

In the last decade, there has been significant parallel progression in the skills and development of finer endourological implements in performing safe and effective percutaneous nephrolithotomy (PNL) or retrograde intra renal surgery (RIRS) for LPC stones. Results in various case series and random controlled trials (RCT) have shown higher success rate and earlier stone-free status by these modalities. The endourological interventions are, however, associated with significant morbidity and is often an overkill for small LPC stone. Incidentally identified asymptomatic stones pose a unique challenge. Some of these stones could at least be managed by deferred treatment. We still do not have quality data to define a trigger for patients with small asymptomatic LPC stones managed conservatively. Stone growth, development of obstruction, infection and pain are some of the well-defined factors to indicate intervention. Proper patient selection with a favourable collecting system anatomy is important for optimal outcome with patients undergoing treatment by shock wave lithotripsy (SWL). Stone burden (>15mm), availability of equipment and expertise, and patient's desire for a single procedure are some valid indication of PNL and RIRS.

Urolithiasis is a common medical condition, with the prevalence rate ranging between 4% and 20% in economically developed countries.[1] There is a significant geographical variation in the prevalence of urolithiasis; it is particularly prevalent in the so-called 'stone belt' areas. The overall prevalence rate in the Chinese population in a recent survey was estimated to be 4.0%, 4.8% in men and 3.0% in women.[2] It is also a highly recurrent condition, with more than half of the patients with previous history of urolithiasis forming another stone in less than a decade.[3] Kidney stones can also cause serious morbidity, pain, hematuria, infection, decreased kidney function and kidney failure. Since its introduction in the 1980s, SWL has become the most minimally invasive treatment option for the renal calculi. Although in the earlier years of its introduction the number of usage was far more liberal, this enthusiasm eventually made way for rational use. There are many factors responsible for achieving optimal stone clearance with SWL. These include stone burden, multiplicity, composition, stone to skin distance and intracalyceal distribution (stone location). Lower pole calyceal (LPC) stone location is one of the most controversial parameters. The current review is focused on the review of existing literature on the controversy surrounding LPC stone clearance.

EVIDENCE SYNTHESIS

What is Wrong with the Lower Pole Calyceal Stone?

Since the time that endourology become the mainstay in the management of nephrolithiasis, LPC stones have been a controversial topic. The debate on the lower pole calyceal anatomy and its impact on stone clearance are as old as SWL itself. Sampaio and Aragao[4] in the early 1990s pointed out that there are factors other than the gravity dependent position of LPC that have an impact on the outcome following SWL. They analysed the LPC anatomy in 146, three-dimensional polyester resin corrosion

endocasts of the pelvicaliceal system. They observed that the inferior pole was drained by multiple calices disposed in 2 rows in more than half of the cases and by 1 midline calyceal infundibulum in over 40% of cases. In about 60%, there was a lower infundibulum > 4mm in diameter and the rest had a lower infundibulum smaller than 4mm in diameter. In about three-quarters of cases, an angle greater than 90 degrees was formed between the lower infundibulum and the renal pelvis, with the remaining cases forming an angle of 90 degrees or smaller. Since urologists have been wary of these anatomical features when considering SWL to treat calculi in the lower calices. Subsequently, studies also demonstrated that an acute pelvic lower pole infundibular angle hinders the spontaneous discharge of fragments after SWL.[6,11,16]

Many techniques have since been proposed for describing the pelvic lower pole infundibular angle. The anatomy of the lower pole is classically studied in an intravenous urogram (IVU). However, IVU is phasing out of the clinical practice as the imaging technique of choice, after having faithfully served the urologist in defining the anatomy of calyx and excretory function of the kidney.[5] Rachid Filho and colleagues[6] recently compared the 3D CT with IVU in defining the anatomy of the pelvicalyceal system, noting that although 3D-HCT is more precise to study calculus location, tumours, and vessels, IVU was also demonstrated to be as precise as 3D-HCT for studying the lower pole spatial anatomy. They did not observe any statistically significant difference in the measurements of infundibulo pelvic angle (IPA), infundibular length and diameter obtained using 3D-HCT when compared with those obtained using IVU, concluding that 3D-HCT does not present any advantage over IVU in the evaluation of lower pole calyceal anatomy. However, since CT is more frequently used in the diagnosis of urolithiasis, additional IVU is not required to define LPC anatomy.

Management of LPC Stones

The options of management include watchful waiting, SWL, RIRS and PNL. Watchful waiting is often recommended for small (<10mm), asymptomatic LPC stones in patients with aseptic urine.[7] Active management is often recommended for stones >10mm. SWL, RIRS and PNL all are valid management options, yet careful patient selection and understanding the limitations of each modality is absolutely necessary in the clinical decision-making.

SWL is the mainstay for the treatment of the majority of small and moderate-sized renal stones in all calyces except LPC.[8] The treatment outcome following SWL depends on the type of lithotripter, patient characteristics like body mass index (BMI), skin to stone distance, stone composition, stone size and intra calyceal distribution. However, one of the most significant factor-affecting outcomes is the stone's characteristics (i.e., number, size, composition and location), renal anatomy, and function. Clearance, rather than stone disintegration of lower pole stones after SWL, is significantly inferior according to other localisations of the kidney. Treatment outcome following SWL depends on type of lithotripter, stone characteristics (i.e., number, size, composition and location), renal anatomy and function.Observations in a meta-analysis by Lingeman et al.,[9] further supported by other reports subsequently published,[10, 11] showed a lower stone-free rate of ESWL for LPC, when compared to results of stones in other calyces. In our previously reported work, we noticed that there was a trend towards more SWL sessions and shock wave requirement in patients with acute pelvicalyceal angle and narrow infundibulum but it is not statistically significant. Size (≤20mm) and BMI has no relation with stone clearance. With modern lithotripter, stones up to 20mm could primarily be treated by SWL, irrespective of an unfavourable lower pole calyceal anatomy and body habitus.

There is dearth of quality RCT comparing the efficacy of the various options of management for LPC stones. Srisubat and colleagues[12] in a Cochrane Systematic Review in 2009 noted that results from three small studies, with low methodological quality, indicated SWL is less effective for lower pole kidney stones than PCNL, but is not significantly different from RIRS. Hospital stay and duration of treatment was less with SWL. More RCTs are required to investigate the effectiveness and complications of SWL for kidney stones compared to PCNL or RIRS.

Outcome of SWL in LPC Stones in Both Adults and Children

There are conflicting reports in literature as to the efficacy of SWL in LPC stones. In the majority of adults' reports significant difference in the stone clearance in between LPC stones and stones located in the other calyces was noted. However, in children most authors have noted insignificant or no differences in outcome. Demirkesen et al.[13] noted that SWL was equally effective for stones in all locations in children. They recommend SWL as the primary treatment of choice for stones less than 2.0cm^2 in all calyceal locations. For the management of calyceal stones greater than 2.0cm^2, prospective randomised trials comparing SWL and PCNL are necessary. Onal and colleagues[14] studied the impact of pelvicalyceal anatomy in stone clearance following SWL in paediatric population and observed that calyceal pelvic anatomy in pediatric lower pole stones has no significant impact on stone clearance after SWL. They observed a highly

Investigators	Number of patients	Mean stone size / Stone burden	Stone-free rate (%)	Impact of unfavourable anatomy
Aboutaleb H[25]	24	15.6mm	62.5	Yes
Albanis S[18]	78	63mm^2	50	Yes
Sahinkanat T[26]	82	11.75mm	62	No
Juan YS[27]	59	10.5mm	57.6	Yes
Ather MH[16]	100	9.4mm	81	Yes
Keeley FX Jr.[28]	116	14.3mm^2	52	Yes
Ghoneim IA[29]	205	65.88mm^2	68	Yes

Table 1: Stone clearance and impact of unfavorable anatomy in the stone clearance rate in the management of isolated LPC renal stone

significant relation between retreatment rates and stone burden, which should be considered for determining the treatment modality. Ather and Noor[15] noted a high stone clearance rate (95%) in renal stones up to 30mm in size. They observed no relation between stone sizes in clearance, yet 3 of 5 children who failed SWL had stones in the lower pole calyx.

The outcome of SWL for isolated LPC stones is detailed in Table 1. The various unfavorable LPC collecting system factors noted in these studies include acute pelvicalyceal angle, long and narrow infundibulum. Ather et al.[16] noted that a trend towards more SWL sessions and shock wave requirement in patients with acute pelvicalyceal angle and narrow infundibulum, but the difference did not reach statistical significance. Size (≤20mm) and BMI has no relation with stone clearance. Arzoz-Fabregas et al.[17] noted that height of the infundibulum, described as the distance between the line passing through the lowest part of the calyx containing the calculus and the highest point of the lower lip of renal pelvis, was the only parameter in which there were significant differences. Various manoeuvers including the application of a vibrating device on the flank, forced diuresis, and inversion therapy are described to improve the outcome of LPC stones. Albanis et al.[18] assessed the efficacy and safety of combined forced hydration and diuresis with limited inversion during (SWL) by comparing this treatment modality with conventional SWL for lower calyceal nephrolithiasis. Clinical outcomes were available in 90 patients. Follow-up at 3 months showed that 83.3% of the patients belonging to the study group were rendered stone-free, whereas 71.5% were stone-free in the control (p>0.05). Complications were minimal and not statistically significant.

Natural History of Small LPC Stone

As asymptomatic stones are increasingly identified due to widespread use of imaging (particularly ultrasonography) it becomes a challenge to devise optimal management strategy for such stones. The natural history of LPC stones is not well-defined and the rate of progression is not clear. There still are no clear recommendations for the frequency, duration and trigger for intervention. The EAU guidelines suggest that although there is no final word on the optimal treatment of calyceal stones, the trigger for intervention include stone growth, de novo obstruction, associated infection and/or chronic pain.[19] Most of these stones are only monitored, however minimally invasive treatment in the form of SWL is also proposed as an alternative.[20] Inci and colleagues[21] studied the natural history of LPC stones and proposed that observation could be considered for patients with asymptomatic lower pole stones. However, patients should be counselled concerning the 33% disease progression and 11% intervention rates.

Asymptomatic renal stones can be followed safely, but long-term follow-up is necessary. Periodic follow-up and early intervention should be recommended in patients with risk factors.[22] Hubner and Propaczy[23] noted that LPC stones are associated with various complications and cannot be indefinitely observed. In their series, 4 out of 5 patients with LPC stone required intervention within five years of diagnosis.

Skolarikos et al.[24] in a meta-analysis concluded that active stone monitoring has a certain role in the treatment of patients with urinary stones. The success is largely dependent on the stone size, location, and composition, as well as the time after the diagnosis. Medical therapy is a useful adjunct to observation.

CONCLUSION

LPC stones continue to be an actively debated subject in the urological community. Optimal management of small uncomplicated, asymptomatic stones is often deferred, however, there are no set points defined to trigger intervention. Patients on deferred treatment require close surveillance, regular clinical and microbiological and imaging work-up. SWL is the most minimally invasive treatment option, however, meta-analysis and RCT have shown lower stone clearance rates. Other endourological options like RIRS and PNL are reasonable alternatives. In experienced hands and in a well-equipped endourological unit, it has a somewhat higher stone clearance rate, while PNL, in particular mini and micro PNL, are reasonable alternatives with a high stone-free rate.

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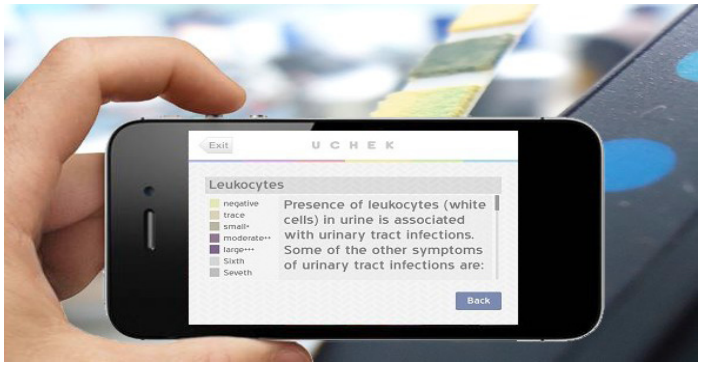
SMARTPHONE APP TESTS URINE FOR MEDICAL ISSUES

UCHEK, a new smartphone application, is able to analyse urine for the presence of up to 10 markers covering 25 different medical conditions. The new app developed by Myshkin Ingawale, a 29-year-old entrepreneur and MIT graduate from India, was presented at the 2013 TED (Technology, Education, and Design) conference in Los Angeles in February, 2013.

The app utilises the smartphone camera to take photos of a chemical strip which is dipped into a urine sample. It then compares them to a colour-coded map and reports the results, showing levels of glucose, bilirubin, proteins, specific gravity, ketones, leukocytes, nitrites, urobilinogen and hematuria present in the urine.

The test results can be helpful for those managing diabetes, in addition to kidney, bladder, and liver problems. The results may also reveal a urinary tract infection.



> "I want people to better understand what is going on with their bodies."
> - Myshkin Ingawale

Currently, the app is undergoing testing in a Mumbai hospital and is currently waiting for approval from Apple. Ingawale says that he hopes the app will soon be available on the iPhone, with an Android version to later follow.

Ingawale has said of an initial testing of 1,200 samples that the app is able to deliver more accurate results than humans looking at the colour strips by eye.

More sophisticated and accurate equipment is available, however these machines are expensive, costing up to $10,000 (£6,600, €7,700). The app itself will cost just $0.99, with an additional cost of $20 for the packet of strips and a colour-coded map.

The idea is to get people closer to their own information," Ingawale says. "I want people to better understand what is going on with their bodies."

SMOKING INCREASES BLADDER CANCER AGGRESSION

SMOKERS have a greater likelihood of developing deadlier and more aggressive bladder cancer, reports a recent study published in the American Cancer Society journal *Cancer*.

The study was led by Dr. Richard J. Cote, of the University of Miami Miller School of Medicine, and Dr. Anirban Mitra, of the Keck School of Medicine of the University of Southern California, who analysed bladder tumours and smoking history in 212 multi-ethnic patients from 1987 to 1996.

Additional results of the study included a panel of nine molecular markers often present in bladder cancers, which can reliably, and independent of other factors, predict cases that are most likely to be deadly. Alterations to six or more of these markers was associated with a very poor outcome.

This has led to a call for personalised patient management from Dr. Cote, Director of the Genitourinary Malignancies Program at University of Miami's Sylvester Comprehensive Cancer Center, as more aggressive treatments may be beneficial for individuals with this prognosis.

EU REGULATOR APPROVES ZYTIGA BEFORE CHEMOTHERAPY

THE European Commission granted approval to expand the use of Zytiga (abiraterone acetate) in prostate cancer to before chemotherapy, following recommendations by the European Medicines Agency's Committee for Medicinal Products for Human Use.

A prescription medicine manufactured by Johnson and Johnson, Zytiga is used to treat men with metastatic castration-resistant prostate cancer (mCRPC) that has spread to other parts of the body, by interrupting androgen production in the testes, the adrenal glands, and the tumour itself.

Jane Griffiths, Company Group Chairman, Janssen Europe, Middle-East, Africa, said: "This decision by the European Commission is hugely welcomed news. It marks another important step forward in the treatment of men with advanced castration-resistant prostate cancer. Treating men with ZYTIGA before they undergo chemotherapy has been shown to improve outcomes in many patients, both in terms of extending survival and in bettering quality of life. The fact that ZYTIGA's licence has now been extended to include this indication will help fill a critical medical need and, we hope, serve to significantly improve the lives of many men across Europe suffering from this disease."

The approval, based on an ongoing Phase III COU-AA-302 study, means Zytiga may now be used alongside prednisone or prednisolone for mCRPC-suffering adults, who are either asymptomatic or mildly symptomatic following a failure of androgen deprivation therapy.

First approved by the U.S. Food and Drug Administration (FDA) in April 2011 after the drug extended median survival to 14.8 months versus 10.9 months placebo during Stage III trials, the FDA cleared an expanded indication for Zytiga in December due to the overall survival and progression-free benefits from the medicine.

Zytiga® abiraterone acetate

MALE CAFFEINE CONSUMPTION LINKED TO LEAKY BLADDERS

BETWEEN 3 and 6 million people in the UK have some degree of urinary incontinence, according to the NHS. A new study suggests that the amount of caffeine contained in a mere two cups of coffee may be a factor in men's incontinence.

While previous research has linked caffeine intake to incontinence in women, a new study has found that males who consumed the most caffeine were more likely to have problems with bladder leakage than those who took the least.

"It's something to consider... People who are having problems with urinary incontinence should modify their caffeine intake and I think that's part of clinical practice," said Dr. Alayne Markland, of the University of Alabama at Birmingham.

The new study, published in The Journal of Urology, looked at responses to a national health survey from 4,000 men between 2005 and 2008, and looked at total caffeine and water intake, from both foods and beverages, in addition to how many of the males had urinary incontinence.

After adjusting for age and other risk factors, the researchers found those who consumed 234 or more milligrams of caffeine daily were 72% more likely to have moderate to severe urinary incontinence, defined as more than a few drops of urine over a month, than those consuming less caffeine.

This trend extended further for those who consumed more than 392 milligrams of caffeine, the report finding those individuals were more than twice as likely to be incontinent. Comparatively, total water intake was not linked to the risk of developing moderate to severe incontinence, suggesting that the quantity of fluid a person consumes is not as important as caffeine intake.

FDA CLEARS ALLERGAN'S BOTOX TO TREAT OVERACTIVE BLADDER, AS FRAUDULENT VERSIONS FOUND IN US MARKETS

U.S REGULATORS approved Allergan's Botox (onabotulinumtoxinA) as treatment for overactive bladder (OAB) symptoms in adults when anticholinergic therapy has failed them.

The toxin, given through a number of tiny injections intended to affect only the problematic area, decreases bladder contractions and blocks signals telling the nervous system that the bladder is full.

The decision to approve the treatment came following two 24-week trials, involving 1105 OAB patients randomly selected to receive Botox or placebo injected directly into the detrusor muscle. Patients treated with Botox experienced at least a 50% reduction in daily urinary incontinence compared to placebo 12 weeks into the experiment.

Results showed 22.9% and 31.4% of patients each respective trial treated with Botox achieved complete elimination of their leakage episodes, compared with 6.5% and 10.3%, respectively, of those in the placebo group. The treatment also lessens the urge to urinate, frequency of urination and the amount of urine voided compared to placebo at week 12, Allergan said.

The approval could add more than $200 million a year to Botox sales according to analysts, with 2011 sales recorded at around $1.6 billion.

Soon after, fraudulant versions of the wrinkle treatment were found in the US market, with the FDA posting an alert on its website, with sales appearing to be solicited by fax rather than online, under the names of 'Online Botox Pharmacy', 'Onlinebotox.com' and 'Onlinebotox'.

CALLS FOR PSA SCREENINGS FOR MEN IN 40s GROW STRONGER

MEN in their late 40s should be offered a prostate cancer screening test, according to researchers. The Swedish team say checking every man aged from 45 to 49 would predict nearly half of all prostate cancer deaths, after studying over 21,000 men.

Professor Hans Lilia and colleagues from Sweden's Lund University and the US Memorial Sloan-Kettering Cancer Center tested for PSA – a protein produced by both normal and cancerous prostate cells – on 21,277 blood samples taken from Swedish men aged from 27 to 52, linking a high PSA with an increased risk of prostate cancer.

Screening men at the suggested optimum age spotted nearly half (44%) of the cancers that went on to become fatal. If put into practice, only those with a high PSA test result would return for future screenings.

"At least half of all men can be identified as being at low risk and probably need no more than three PSA tests in a lifetime," they say in the British Medical Journal.

"This is likely to reduce the risk of over-diagnosis while still enabling early cancer detection among those most likely to gain from early diagnosis."

> "At least half of all men can be identified as being at low risk and probably need no more than three PSA tests in a lifetime."
> - Professor Hans Lilia

While one European study suggests deaths from prostate cancer could be reduced by 20% were a screening programme introduced, only one extra life would be saved for every 48 treated.

Screening remains a controversial subject in urology due to the unreliable nature of the PSA tests, which can falsely suggest the presence of cancer and result in men receiving unnecessary invasive biopsies.

While PSA remains a favoured method, around 15% of men with normal PSA levels will have prostate cancer, and two-thirds of men with high levels of PSA do not have prostate cancer at all.

GENETIC ALTERATIONS CAN IDENTIFY BLADDER CANCER RISK, RECURRENCE AND PROGRESSION

A RECENT article published in Cancer, a journal of the American Cancer Society, published findings which could help improve bladder cancer screening and treatment. Dr. Eugene Lee of the MD Anderson Cancer Center in Houston, and his colleagues worked together with Dr. Xifeng Wu's Epidemiology Lab, to compare 803 bladder cancer patients with 803 healthy individuals.

Both patients with non-muscle invasive and those with muscle invasive bladder cancer were included in the study, which determined the role of regulators of G-protein signalling (RGS) alterations in risk, recurrence, disease progression, and patient survival for bladder cancer.

After evaluating 95 single nucleotide alterations or variants in 17 RGS genes, the investigators identified several that were linked with overall risk of bladder cancer. The strongest association was seen with the rs10759 variant on the RGS4 gene: it was linked with a 0.77-fold reduced risk of overall bladder cancer. The researchers also found that with an increasing number of unfavourable variants, the risk of bladder cancer increased.

"Screening for bladder cancer has proven to be difficult on a population level, and our work may be a first step in identifying molecular markers for potential genetic-based screening tests. This will help recognise specific groups at increased risk beyond the existing known risk factors such as smoking and chemical exposure," said Lee.

Lee and his team also revealed that in patients with non-muscle invasive bladder cancer, 11 variants were linked with recurrence and 13 variants were linked with progression. 10 variants were associated with earlier death in patients with muscle invasive bladder cancer; rs2344673 was the most significant, with an average survival of 13.3 months in patients with the variant compared with 81.9 months in patients without it.

In the current era of personalised medicine, an individual's genetic information can provide valuable knowledge on screening, treatment, and surveillance. "Our study provides an initial step in how we can use a patient's genetic makeup to identify those at risk for bladder cancer. Furthermore, we can identify patients who already have a diagnosis of bladder cancer that are at increased risk of worsening of disease or dying from their cancer," said Lee. "The goal is to find as many genetic alterations that confer risk and create a panel of markers that would aid in diagnosis, treatment, and follow- up."

GIVE PATIENTS A CHOICE IN CATHETERS, URGES RESEARCHERS

A RECENT study suggests that patients utilising catheters for urinary retention should be offered the choice between clean non-coated, hydrophilic, or gel reservoir catheters, after researchers found few differences between catheter type and risk for symptomatic urinary tract infections (UTIs). This was found in a systematic review and meta-analysis by Sarah Bermingham, of the Royal College of Physicians, London, of eight eligible studies, mainly of patients with spinal cord injuries.

UTIs associated with catheter use is a leading cause of morbidity and mortality in individuals using urinary catheters. In the report, clean non-coated catheters were found to be the most cost-effective, followed by gel reservoir, and then hydrophilic catheters. However, the authors do state that the evidence base is limited, and individual patients may find one type of catheter more comfortable or easier to use, benefits that were not explored within the study.

"Additional data about the incidence of infection, urethral complications, patient compliance, methods of cleaning catheters, and quality of life are needed before such a change in practice is implemented," the authors say.

IMMUNE MEMORY DEFECT MAY CAUSE REPEAT BLADDER INFECTIONS FROM SAME STRAIN OF BACTERIA

A DEFECT within the bladder's immunity response that can prevent it from remembering previous bacterial infections may be responsible for recurrent bladder infections. This lapse in memory can prevent a timely attack, according to researchers at Duke Medicine and Duke-National University of Singapore. A muted immune response to bacterial infection can mean that a persistent population of bacteria is not fully eradicated, allowing reinfections from the same strain of bacteria.

"A third of recurring bladder infections are from the same strain of bacteria, so that suggested to us that there is some sort of defect in the bladder that is causing this," said Soman N. Abraham, PhD, senior author of the paper, which was published in the journal Immunity. "We have identified how a muted immune response to bacterial infections in the bladder occurs, making it unable to fully eradicate a persistent population of bacteria."

Abraham and his team examined mouse bladders under conditions very similar to human infections; they found that UTIs were generally met with a robust inflammatory response from the innate immune system. This was regardless of whether the infections remained in the bladder or travelled to the kidneys.

> "It appears that the bladder, like the gut, has a highly specialised strategy for balancing tolerance and resisting infection."
> - Soman N. Abraham, PhD

However, after a period of 21 days, when the mice were re-infected, a strong antibody response from the immune system was only observed in the group of mice where both the bladder and kidney were infected, and not in the group of mice that had just the bladder infection showed.

This suggests that in the first group of mice, their immune systems were able to recognise the pathogen and were thus able to quickly and effectively eradicate it. The cause of this has been attributed to mast cells, cells best known for fighting allergies. The cells always acted when confronted with the infection, but in some cases, they produced interleukin-10, a molecule which supresses the immune system, preventing the immune system from forming antibodies that would be able to recognise a future invasion of the same pathogen.

"It appears that the bladder, like the gut, has a highly specialised strategy for balancing tolerance and resisting infection," Abraham said. "In most cases, muting the adaptive immune response in the bladder would not be a problem, because the infection would be cleared by the vigorous response of the early, innate immune response. But in some people, it's causing recurrent infections, because the bacteria hide in the epithelium and are not recognised by the adaptive immune system."

Abraham has suggested the findings of the research could lead to the development of vaccines against the bacteria, or potentially result in superior treatments which would reinforce antibody response.

SCHIZOPHRENICS 29 TIMES MORE LIKELY TO HAVE UTI

SCHIZOPHRENIA patients experiencing relapse are 29-times more likely to suffer from urinary tract infections (UTIs) compared to healthy individuals.

The study, written by Dr. Brian J. Miller, psychiatrist and schizophrenia expert at the Medical College of Georgia at Georgia Regents University in Journal of Clinical Psychiatry, suggests that relapsing patients should be tested for UTIs.

After observing 57 hopsitalised patients who had relapsed, compared to 40 stable outpatients and 39 healthy controls, results showed that 35% of the relapsed patients had UTIs, as opposed to 5% and 3% of the other groups respectively The trend is believed to be due to schizophrenic relapse producing delusions and symptoms, which can affect a person's handling of their hygiene. The study was sparked after revelations that dementia sufferers see their condition improve while take antibiotics in order to combat UTIs.

"The questions we are asking is, 'Does that same phenomena seem to take place in patients with schizophrenia?" and we are finding evidence that it does," Miller said.

NEW TREATMENT OPTION FOR OVERACTIVE BLADDER PATIENTS BOTHERED BYANTIMUSCARINIC SIDE EFFECTS

A NEW phase III trial of mirabegron, a β3-adrenoceptor agonist, given once daily for twelve weeks, reduced the frequency of incontinence episodes and number of daily urinations, while improving urgency and nocturia in adults with overactive bladder (OAB) compared to those in a placebo condition.

"Mirabegron is a first in class therapeutic agent with a mechanism of action distinct from that of antimuscarinic agents," says urologist Victor W. Nitti, MD, of the NYU Langone Medical Center. "While antimuscarinic agents are the current pharmacological mainstay for OAB some patients have a suboptimal response or experience side effects such as dry mouth or constipation. The result is that a high proportion of patients on antimuscarinic drugs discontinue therapy, with only 25% remaining on therapy at one year. We need an alternative therapy for some of these patients."

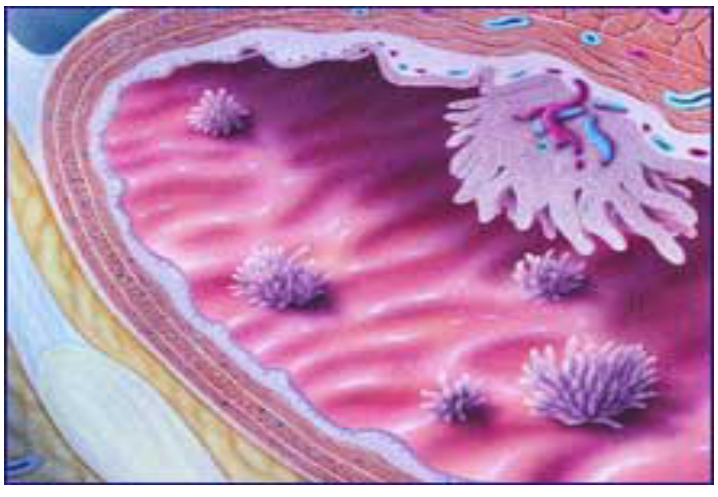
This randomised, parallel group, double-blind phase III study, published in The Journal of Urology, was comprised of 1329 patients. Those eligible for the study voided 8 or more times daily and experienced 3 or more urgency episodes with or without incontinence over a 30 day period. After 2 weeks of receiving placebo, 454 patients were randomised to continue receiving placebo, 442 received 50 mg mirabegron, and 433 received 100 mg mirebegron daily for 12 weeks.

Both mirabegron treatment groups showed significant ($P < 0.05$) reductions in the mean number of episodes of incontinence and micturition per period of 24 hours, and increases in the average volume voided, from an average of 7.0 ml to around 18ml. This finding supports the hypothesis that β3-adrenergic agonists work by promoting urine storage and increasing bladder capacity. This occurs by mirabegron activating the β3-adrenoceptor receptor in the detrusor muscle in the bladder, relaxing the muscle.

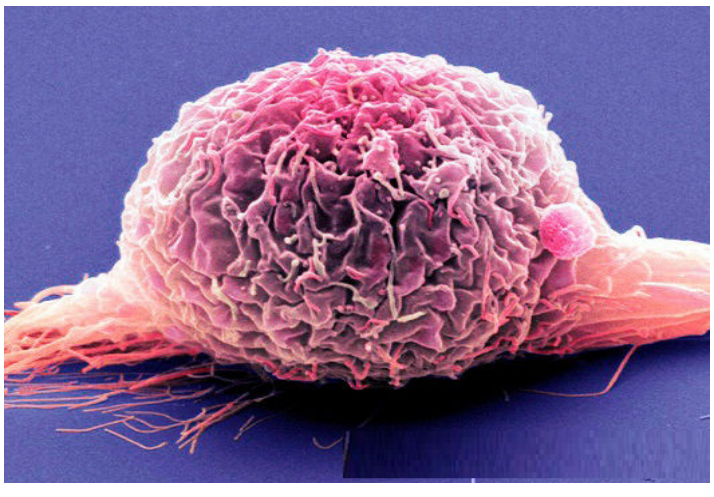
> "A high proportion of patients on antimuscarinic drugs discontinue therapy...We need an alternative therapy."
>
> - Victor W. Nitti, MD

Additionally, urgency and nocturia were reduced in both mirabegron treatment groups, compared to placebo. Significant improvements were found in quality of life measures, and the effect size of the treatment was similar to that seen by other overactive bladder agents.

Treatment-emergent adverse events (hypertension, urinary tract infection, headache, nasopharyngitis, dry mouth, constipation) were low and were reported at similar levels in both the mirabegron and placebo groups.



Cancer growths in the bladder



Superficial bladder cancer growth

COENZYME Q10 SUPPLEMENT MAY BOOST MALE FERTILITY

TAKING A three month course of coenzyme (CoQ10) supplements could improve semen quality among infertile men, a recent study suggests.

In a study of 47 men with oligoasthenoteratozoospermia (OAT), those who took the supplement had reduced levels of oxidative stress and improved activity of antioxidant enzymes in the seminal plasma after 3 months, compared with men who took placebo.

CoQ10 is a powerful antioxidant and some trials have shown it can improve sperm quality in subfertile men. However, no studies have yet reported its effects on the activity of antioxidant enzymes such as catalase and superoxide dismutase (SOD) in seminal plasma, say Mohammad Sadeghi and colleagues.

The study, as reported in Andrologia, reports that taking CoQ10 200 mg daily significantly increased the men's mean seminal plasma level of CoQ10, from a baseline of 44.7 ng/mL to 68.2 ng/mL, at the end of the study.

There was a significant positive correlation between CoQ10 concentration and normal morphology of spermatozoa, and CoQ10 was also modestly but significantly correlated with the forward motility of sperm.

The researchers report that the men in the supplement group had a significantly higher mean seminal plasma level of catalase and SOD activity than those in the placebo group after 3 months, and the level of CoQ10 significantly correlated with the activity of both these enzymes.

Further analysis showed that the mean seminal plasma level of the oxidative stress biomarker 8-isoprostane significantly fell from baseline following CoQ10 supplementation compared with the placebo group.

HERPES SIMPLEX VIRUS VECTOR OFFERS NOVEL TREATMENT APPROACH IN TREATING SUBSTANCIAL BLADDER PAIN

AN ALTERNATIVE strategy for treating severe chronic pain associated with conditions such as interstitial cystitis (or bladder pain syndrome) has been described in a recent article in Human Gene Therapy.

The treatment, which increases the levels of a naturally occurring painkiller, is a departure from the common use of opioid medication, which carries risks of dependency and other serious adverse reactions.

This new therapeutic approach is a gene therapy technique in which the gene for enkephalin is injected directly into the bladder wall, an opioid compound produced by the human body. The gene is transported into the target cells via a herpes simplex virus vector that is incapable of replication. This naturally occurring painkiller is present in and around the nerves that deliver pain signals to the bladder.

The study, conducted by Hitoshi Yokoyama and colleagues, from University of Pittsburgh School of Medicine, Shinshu University School of Medicine, and Diamyd (Pittsburgh), showed that high levels of enkephalin gene expression in treated rats and significantly lower measures of pain when exposed to stimuli intended to induce bladder irritation.

The researchers noted that a similar gene therapy delivery vector carrying an enkephalin gene has been used in human clinical studies to treat cancer-related pain, and was shown to be well-tolerated and safe and to provide substantial pain relief.

"This is a very innovative application of Herpes Simplex Virus gene therapy in the treatment of a common and painful clinical problem that otherwise requires chronic use of narcotics," said Dr. James M. Wilson, Editor-in-Chief, and Director of the Gene Therapy Program, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia.

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6th EAU Leading Lights in Urology (LLU)

June 6-8, 2013

Lisbon, Portugal

This is an academic forum set to explore all aspects of urology in a pleasant, relaxed environment, with a particular emphasis on critical discussion of important and sometimes controversial topics, allowing extensive interaction between the faculty and audience. forum for interaction, collaboration and will hopefully lead on to innovative research opportunities within the field of academic urology in Europe.

1st International Uroanatomy Congress

June 14-16, 2013

Izmir, Turkey

This Congress is the first in the world, and is set to be a biennial event held in different countries. The topics that have been announced are Basic Uroanatomy and Uroembryology, Surgical and Techniqual/Minimal Invasive Uroanatomy, Radiologic and Sectional Uroanatomy, and Microscopic and Pathologic Uroanatomy.

EAU Robotic Urology Section Congress

Latest Developments in Robotic Surgery

June 3-5, 2013

Stockholm, Sweden

This year, Stockholm, Sweden will be hosting this exciting event that educates the urological community in robotic surgical techniques with the ultimate aim of improving the level of patient care. The meeting will inolve live surgeries of both standard procedures and new indications in HD and 3D, in addition to state-of-the-art lectures.

3rd International Meeting "Challenges in Endourology and Functional Urology

June 26-28, 2013

Paris, France

The Meeting has been established as a highly educational scientific meeting offering a programme full of innovation, knowledge exchange and valuable networking. There are a variety of session types including the highly educational workshops and live surgery sessions, in addition to the opportunity for researchers to present their work through e-poster presentations.

86th Annual Meeting of the Società Italiana di Urologia (SIU)

October 5-8, 2013

Riccione, Italy

The 86th SIU Congress will be an opportunity to listen and to share the latest news on the main topics in the field of urology. There will be a combination of plenary, poster, and live surgery sessions, interactive courses, and hands on workshops throughout the Congress.

Urology Week

September 23-27, 2013

Across Europe and beyond!

Urology Week is an initiative of the European Association of Urology, which brings together national urological societies, urology practitioners, urology nurses and patient groups with the aim to create awareness of urological conditions among the general public. Each year, educational and media events take place throughout this week all across Europe, and even further afield.

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